Critical Care Reviews Book 2022

The Best Critical Care Trials of 2021

First Edition


Critical Care
Reviews

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About

The Critical Care Reviews Book 2022 seeks to summarise, critique and put in context the best critical care trials of 2021. Five intensivists working in the Belfast Health and Social Care Trust have spent the past six months writing this year's edition. It is also not yet complete, as both the COVID-19 section remains to be added, as do a few other trials we ran out of time to include. We aim to put out a second edition of this year's book later in the Autumn

Our choices are largely subjective and clearly some major studies may have been excluded, but we feel we have captured the essence of the critical care research output from the past 12 months. We hope you enjoy this work and find it useful in your daily practice. Please read the disclaimer at the bottom of this page.

The print version of the book has once again been very generously sponsored by the REVIVE charity of the Regional Intensive Care Unit at the Royal Victoria Hospital in Belfast. Every registered delegate at the annual Critical Care Reviews Meeting receives a complimentary copy. Rob Mac Sweeney is also supported by Charitable Funds from the Belfast Health and Social Care Trust to aid his dissemination work with Critical Care Reviews.

The authors are grateful for the proof reading and comments made by our colleague Peter McGuigan.

We would love to hear any feedback you may have on this book. All correspondence will be gratefully received at rob@criticalcarereviews.com

Rob Mac Sweeney
Critical Care Reviews

Belfast,
June 2022

Disclaimer:

This book aims to summarise the major critical care trials of 2022. Although care has been taken to ensure information is correct, this is not guaranteed and no responsibility is accepted for clinical decisions based on material within this book. Clinicians are advised to check the primary literature at all times. The opinions stated within this book do not constitute clinical advice. They are opinions, not fact, and others may take a different view of our interpretations of these trials. Please refer to the appropriate clinical guideline issued by the relevant society or scientific body for the management of any specific condition.

Foreword

How to provide the best possible care to our patients? How to decide between two potential interventions? Evidence-based medicine can help us to make the best decision at the bedside. Randomized control trials (RCTs) provide answers to important clinical questions and only randomization can properly balance the unmeasurable factors that may influence the response to interventions. They are not perfect, and we are still struggling with our failures. Novel insights, such as adaptive designs, Bayesian analysis and patients and families-centered outcomes, are new steps towards the future in our field. Enrichment strategies, aimed at assessing patients' characteristics which can guide enrollment criteria and enhance the likelihood of a positive trial based on patients' susceptibility to either the intervention or to the outcome, might also result in better trials. We treat individuals, not populations. Thus, care should be individualized, although based on the best available evidence produced for that group of patients.

However, to bring this high-quality evidence to the healthcare worker at the bedside is a challenge. Knowledge should not be anyone's property. Restricted access to knowledge leads to disparity, as many cannot afford it. Why should patients in the poorest parts of the world not be treated by healthcare professionals with full access to high-quality information? We need equal access to knowledge worldwide. Unfortunately, the barriers for open access are huge. Fortunately, Free Open Access Medical education (FOAM) has grown considerably in recent years, thus providing access to highly-qualified materials which can improve education through non-traditional methods. This is certainly important to those living in developed countries. However, in terms of equity, this is even more relevant to those who cannot afford the high costs of information. Considering that 85% of the world's population lives in low and middle-income countries, we envisage how many would benefit from open access initiatives. Unfortunately, language is a limitation.

Finally, as our final aim is to provide better care, RCTs should preferably be easy to read and to understand. Unfortunately, this is far from being true. Trialists and others who are deeply involved in the generation of evidence might not perceive how complex reading an RCT can be to those who are not skilled at it and did not have adequate training. Making it simple without losing sight of its essence is an art.

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Flavia R Machado
Professor and Chair of Critical Care Department
Anesthesiology, Pain and Critical Care Department
Universidade Federal de São Paulo
São Paulo, Brazil

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Neuro Trials

Vourc'h M, Garret C, Gacouin A, Lacherade JC, Jonas M, Klouche K, et al. Effect of High-Dose Baclofen on Agitation-Related Events Among Patients With Unhealthy Alcohol Use Receiving Mechanical Ventilation: A Randomized Clinical Trial. JAMA 2021;325(8):732-741

Introduction

Delirium and agitation are common problems in critical care, affecting up to 65% of patients, and crucially is associated with increased mortality and poorer long-term cognitive outcomes.[1] It is a complex condition, with a multifactorial pathophysiology. There are multiple risk factors, including age, coma or neurological diagnosis, treatment with sedative medications, increased severity of illness and substance abuse.[1] In particular alcohol abuse is associated with increased agitation and delirium and a higher risk of death in the ICU.[2] Alcohol enhances the brain's main inhibitory systems via the Gamma-Aminobutyric Acid (GABA)-A receptor. It also suppresses the excitatory system via antagonism of the N-Methyl-D-aspartic acid (NMDA) receptor leading to the overall central nervous system depressant effect. Chronic exposure to alcohol leads to down-regulation of the GABA-A receptors and upregulation of the NMDA receptors. Abstinence or withdrawal causes the balance between GABAergic and glutaminergic systems to reverse with decreased inhibition and increased central nervous system excitation.[3]

The prevalence of alcohol withdrawal syndrome (AWS) in general ICU populations ranges from 0.5% to 8%, but maybe as high as 52% among patients with alcohol-related admissions.[4] Treatment guidelines for alcohol withdrawal recommend the use of benzodiazepines as a gold standard.[5] However, benzodiazepines are not recommended for sedation in critical care patients and have been associated with increased delirium.[1,6]

Baclofen is a GABA-B receptor agonist and has the potential to suppress alcohol withdrawal syndromes and alcohol related agitation. It is mainly renally excreted and therefore may have an advantage in liver failure patients. Baclofen has been used to treat alcohol misuse and withdrawal syndromes in non-critical care settings, although the evidence base remains limited with the efficacy, ideal dosing and proper patient selection still to be elucidated.[7] Furthermore, the use of baclofen in critical care for the treatment of agitation in patients with a history of alcohol excess has not been previously investigated. The BACLOREA trial was therefore a novel concept with a plausible biological rational.

Synopsis

This multi-center, double blind, randomised controlled trial was performed in 18 ICUs in France and compared the use of baclofen with placebo for the prevention of agitation in critically ill patients with a history of alcohol abuse. Adult patients expected to require ventilation for more than 24 hours and who met the US National Institute on Alcohol Abuse and Alcoholism (NIAAA) criteria for unhealthy alcohol use, and were able to have enteral treatments, were eligible for recruitment. Unhealthy alcohol use was defined as consumption of more than 14 units per week for men and 7 units per week for women (where one unit approximates to a small glass of wine or tin of beer). Alcohol intake was gained from either the patient, relative or medical record. Patients were excluded if they had been administered baclofen, or had baclofen intolerance, had a history of treatment-resistant epilepsy or epileptic seizure in past 6 months; had porphyria, celiac, or Parkinson disease; were admitted for burn treatment; had brain injury due to recent stroke or haemorrhage; had quadriplegia or paraplegia; had cardiac arrest; had a tracheostomy on ICU admission; had a hospital stay of at least 7 days prior to randomization; had mental impairment (such as dementia, schizophrenia, bipolar disorder, severe depression); or had health care limitation due to poor prognosis. Pregnant patients were also excluded.

Patients were centrally randomised in a 1:1 ratio using a computer-generated sequence stratified by center to receive baclofen or placebo. Identical blister packs were prepared by Nantes University Hospital pharmacy to ensure blinding. The patients received a loading dose of trial drug, ranging between 50 to 150 mg. This was based on the estimated glomerular filtration rate (eGFR). Subsequently, from day 2 to 15, they received 50 to 150 mg per day in three divided doses, again based on renal function. After day 15, the drug was gradually reduced over the next 3 to 6 days. The trial drug was discontinued if the patient was extubated, had a tracheostomy or were discharged from the ICU. For safety, the trial drug could be temporarily stopped if the eGFR fell below 15 mL/min/1.73 m^2, aminotransferase enzyme level was more than 20 times greater than the reference range, or heart rate was less than 50/min. The trial drug was permanently stopped if the patient developed allergic symptoms, mydriasis or had a seizure, stroke, heart rate less than 35/min, or delayed awakening (defined as no eye opening 72 hours after cessation of other sedatives and analgesics). A nurse led sedation protocol, aiming for a Richmond Agitation Sedation Scale score of –2 to +1 was used and agitation was assessed using the Riker Sedation-Agitation Scale. Symptoms of alcohol withdrawal were assessed using the revised Clinical Institute Withdrawal Assessment of Alcohol Scale. Protocol adherence was assessed by the ratio of the dose administered versus the protocol specified dose.

The primary outcome was the occurrence of a least 1 agitation-related event over the treatment period. Agitation events were defined as unplanned extubations; pulling out lines, catheters, or drains; falling out of bed; absconding from the ICU, immobilization device removal; self-aggression; or aggression toward medical staff. Secondary outcomes included the occurrence of at least 1 agitation-related event up to 28 days, agitation requiring rapid administration of hypnotic or neuroleptic drug, extubation failure (defined as reintubation within 48 hours after extubation), need for tracheotomy, reintubation by day 28, ICU-acquired infection, cumulative doses of psychotropic drugs in the ICU, Riker Sedation-Agitation Scale score from day 1 to 28, CIWA-Ar score from day 1 to day 7 after extubation or tracheotomy, duration of ICU stay, duration of hospital stay, ICU, hospital and 90 day mortality, duration of mechanical ventilation, and number of days alive without mechanical ventilation during the first 28 days.

Based on a reported incidence of agitation in low risk alcohol users of 31% and 42% in patients with unhealthy alcohol intake, recruitment of 314 patients was required to detect a 15% reduction in agitation events in the baclofen group using a 2-sided test and 80% power. In the primary analysis, all patients were analysed according to their randomisation group using a center-adjusted logistic regression model, with center as the random effect. Missing data for the primary outcome were handled by multiple imputation methods (10 imputations; relative efficiency >99%).

Over a 30-month period, in total 25294 patients were screened; 15245 were excluded as they were not expected to be ventilated more than 24 hours, a further 13099 did not meet the alcohol intake threshold, and 1832 met other exclusion criteria, including unavailability of the research team for a small percentage. 314 patients were randomised, with 3 patients later excluded. Patient characteristics in the two groups were similar at baseline, with a slightly higher rate of alcohol abuse in the baclofen group. Of the 314 patients, 253 (80.6%) were men and 247 (78.6%) were admitted for an underlying medical condition. The mean SAPS II score was 47.7 and the median (IQR) alcohol intake was 6.0 (4.0-10.0) units per day. Study participants received 92% of the total protocolized dose, although the percentage of patients with 100% adherence to the treatment protocol was just 33.6% in the baclofen group and 44.3% in the placebo group.

77 patients had at least 1 agitation-related event over the treatment period. The percentage of patients with at least 1 agitation-related event was significantly lower in the baclofen group than in the placebo group (19.7% vs 29.7%; absolute difference, –9.93%; 95% CI, –19.45 to –0.42). In a second sensitivity analysis in which all patients who died during the treatment period were considered as having at least 1 agitation-related event, there was no significant difference between the groups for the primary outcome.

By day 28, the percentage of patients with at least 1 agitation-related event did not differ significantly between groups, 27.8% in the baclofen group and 34.8% in the placebo group, although the total number of agitation events was lower (70 vs 111 events).

Amongst the secondary outcomes, patients in the baclofen group had significantly fewer ventilator free days (median of 14.0 vs 19.0 days; difference, –2.00; 95% CI, –4.00 to 0.00). They also had significantly longer median duration of mechanical ventilation (9.0 vs 8.0 days) and longer ICU stay (14.0 vs 11.0 days). The baclofen group also spent more time (mean of 7.0 vs 4.6 days) with a Riker Sedation-Agitation Scale score between 1-3 indicating deep sedation. There was no difference in the use of rescue medications, nor was there any significant differences in the rates of reintubation, tracheostomy, and ICU-acquired infections or 28-day mortality.

Adverse events requiring drug discontinuation (14.6% vs 4.5%) and delayed awakening requiring study drug discontinuation (8.9% vs 1.9%) occurred more often in the baclofen group.

Critique

Excess alcohol has been associated with up to 20% of admissions to the ICU.[4] Despite this heavy burden on critical care resources, there is a paucity of research data on identification, prevention, or optimum treatment strategies for critically ill patients.[4] Benzodiazepines are considered first line treatment for alcohol withdrawal, and are prescribed based on the symptoms and severity of this condition.[5] Use of benzodiazepines in critical care using symptom-based strategies has been shown to be effective, but not all patients can be easily clinically assessed for withdrawal symptoms after intubation and ventilation.[8,9] Furthermore, the use of benzodiazepines for sedation, in comparison to shorter acting propofol or dexmedetomidine, has been associated with longer ICU stay, increased duration of ventilation and increased rates of delirium.[1] Both propofol and dexmedetomidine have been successfully used to treat alcohol withdrawal.[10,11] A trial therefore investigating alternative treatments in the intensive care is a valid and reasonable endeavour.

The BACLOREA trial investigated the use of baclofen, a GABA type B agonist. Baclofen has been recommended as a second line agent for abstinence in alcohol use disorder, where it has been trialled, mainly using doses less than 30 mg/day, with variable success.[7,12] Higher doses have been used, but generally with slow titration due to baclofen related side effects.[7] The dose of baclofen in the BACLOREA trial was 50-150 mg/day depending on renal function. Although this is a high dose, the trialists had previously conducted a pharmacokinetic trial to establish dosing in critical care,

particularly in renal impairment. When monitored for toxicity in this preliminary trial, drug levels were well below toxic levels.[13] However, although the baclofen group did not have major adverse effects, they were more deeply sedated and for longer than the placebo group (with a Riker Sedation-Agitation Scale score between 1-3 for a mean of 7.0 vs 4.6 days). This was despite a protocol recommending light sedation. Doses of other administered sedatives did not different between groups. The baclofen group had a longer median duration of mechanical ventilation (9.0 vs 8.0 days; difference, 2.0 days; P = 0.02) and longer length of stay in the ICU (14.0 vs 11.0 days; difference, 2.0 days; P = 0.01). Although mortality was not significantly increased, it was higher. While the trial intervention did reduce agitation events, it seems at the expense of deeper sedation, with an unresponsive patient less likely a patient to pull out an endotracheal tube. At 28-days the percentage of patients with an agitation event did not differ significantly, suggesting that when sedation was lightened, patients in the baclofen group experienced similar agitation. Overall event rates were however reduced, implying baclofen has some effect.

The optimal dose from the study is not clear, given that increased sedation a lower dose may have been more appropriate. The BACLOREA trial also used a fixed dose regime, only adjusted for renal impairment. Treatment of alcohol withdrawal more usually adjusts doses according to symptom control, and this approach has been successful in critical care, but also highlights the problem of assessment of alcohol withdrawal symptoms in ventilated patients.[8,9] The revised Clinical Institute Withdrawal Assessment for Alcohol Scale, which was only used after extubation in this trial, and the Sedation Agitation Scale, have been used, but the evidence for improved outcomes in ventilated patients is lacking.[4] Again, further research maybe required to find the best dosing regimen for baclofen in critical care patients.

Another problem with alcohol withdrawal syndrome research is the prediction of patients who will develop the condition. The most common general screening tool is the CAGE questionnaire.[14] However this questionnaire has limited ability to predict severity or outcome in critically ill patients and many patients are not able to be questioned on their alcohol habits.[4] The BACLOREA trial used the US National Institute on Alcohol Abuse and Alcoholism criteria for unhealthy alcohol use (>14 units per week for men and 7 units per week for women or men older than 65 years). The median (IQR) alcohol intake was 6.0 (4.0-10.0) units per day, with 75% of patients reportedly drinking at least 4 drinks per day. Although these consumption levels suggest alcohol abuse, they do not clearly define a high risk of alcohol withdrawal syndrome population.[4] The rates of agitation in the trial were lower than predicted in both groups, suggesting the recruited patients were not quite the high risk population that might have benefited most from

the trial intervention. In a post hoc analysis, patients with the highest alcohol consumption had the greatest reduction in agitation with baclofen.

A further potential consideration with a lower risk population and lack of screening tools for alcohol withdrawal is the overlap with delirium. In the ICU, delirium may be the most commonly encountered diagnosis, with a reported prevalence as high as 60%.[1] Alcohol abuse is also a risk factor for the development of delirium.[15] While there may be features common to both, delirium and alcohol withdrawal should be differentiated as treatments differ; benzodiazepines are recommended for alcohol withdrawal but should probably be avoided in delirium.[1,5] The BACLOREA trial primarily focused on agitation, which is also consistent with hyperactive delirium. Pure agitated delirium affects less than 2% of patients with delirium in the ICU, but mixed delirium affects the majority of delirious patients and it is likely that some of these patients had delirium rather than alcohol withdrawal[1]. Perhaps the use of a screening tool like CAM-ICU, might have identified patients who had other features more consistent with delirium, such as hypoactive features, rather than alcohol withdrawal. This would add further complexity to the trial, but there is no evidence for the use of baclofen in the treatment of delirium.

Finally, there are multiple pharmacological interventions for the potential treatment of alcohol withdrawal.[4] Many of these agents are used routinely in the ICU for sedative management. Patients in the BACLOREA trial were exposed to multiple different agents; in particular, two-thirds of patients had midazolam and propofol, meaning the trial compared baclofen in addition to these other agents. In hindsight, now armed with the knowledge generated by BACLOREA, perhaps a future trial comparing baclofen to benzodiazepines (as the gold standard) with a standardised sedation protocol might be worth considering.

Where this sits in the body of evidence

In a single centre, open-label, randomised trial, 37 patients with alcohol withdrawal syndrome were randomised to baclofen (30 mg/day for 10 days) or to diazepam (0.5-0.75 mg/kg/day for 6 days). The Clinical Institute Withdrawal Assessment (CIWA-Ar) was used to evaluate physical symptoms of AWS. Both baclofen and diazepam significantly decreased CIWA-Ar score, without significant differences between the 2 treatments. Both treatments decreased the agitation score, although diazepam was slightly more rapid than baclofen.[16]

In a double-blind, two centre, randomised controlled trial, 44 patients who developed alcohol withdrawal symptoms, whilst on a symptom triggered benzodiazepine treatment protocol, were randomised to treatment with 10 mg three times daily of baclofen or placebo. Just 31 patients completed follow up. The need for high doses of

benzodiazepines (>20 mg of lorazepam over 72 hours) was reduced in the baclofen group (6% vs 54%, P=0.004).[17]

In a single centre open label randomised trial, 60 patients with alcohol withdrawal syndrome were randomised to receive baclofen (30 mg) or chlordiazepoxide (75 mg) in divided doses for 9 days. Clinical efficacy was assessed by the Clinical Institute Withdrawal Assessment for Alcohol-Revised Scale. Lorazepam was used as a rescue medication. Baclofen and chlordiazepoxide showed a consistent reduction in the total CIWA-Ar scores. However, chlordiazepoxide showed a faster and more effective control of anxiety and agitation, requiring less lorazepam supplementation (9 vs 17 patients).[18]

In a single centre, blinded , randomised controlled trial, 159 trauma patients with chronic alcohol abuse were randomised to treatment of alcohol withdrawal with either flunitrazepam/clonidine (n=54); chlormethiazole/haloperidol (n=50); or flunitrazepam/haloperidol (n=55). All patients, with the exception of 4 patients in the flunitrazepam/clonidine group, responded to treatment with a revised clinical institute withdrawal assessment for alcohol scale below twenty. Mechanical ventilation was significantly prolonged in the chlormethiazole/haloperidol group (P=0.0315) due to an increased frequency of pneumonia (P=0.0414). Cardiac complications were significantly increased in the flunitrazepam/clonidine group (P=0.0047).[19]

In a double-blind, randomised controlled trial in a surgical ICU, 44 patients who developed AWS were allocated to either a continuous regimen of intravenous drug therapy or an as required intravenous regimen. The continuous therapy group received an infusion of flunitrazepam, and regular doses of clonidine and haloperidol. The as required group received the same medications bolused in response to the development of the signs and symptoms of AWS. The severity of AWS did not differ between groups initially, but significantly worsened over time in the infusion-titrated group. This required a higher amount of flunitrazepam, clonidine, and haloperidol. ICU treatment was significantly shorter in the bolus-titrated group (median difference 6 days) due to a lower incidence of pneumonia (26% vs 43%).[20]

In a single centre trial, 26 critically ill surgical patients with AWS were randomised to clomethiazole (CLO) or gamma-hydroxybutyric acid (GHB). GHB was more effective in treating AWS symptoms. In the GHB group, AWS score dropped from 6.6 ± 2.6 to 1.8 ± 2.1 (P <0.01), while in the CLO group, the score dropped from 6 ± 2.5 to 4.1 ± 2.4 (P > 0.05). Differences between groups were significant (P=0.021, two-way ANOVA). The treatment did not alter outcome or the duration of ICU stay. No serious side effects were detected.[21]

In an American single centre, double-blind, placebo-controlled trial, 24 adult patients with a Clinical Institute Withdrawal Assessment score greater than or equal to 15, despite at least 16 mg of lorazepam over a 4-hour period, were randomised to dexmedetomidine 1.2 µg/kg/hr (high dose), 0.4 µg/kg/hr (low dose), or placebo as adjunctive therapy for up to 5 days. The difference in 24-hour lorazepam requirements after versus before study drug was greater in the dexmedetomidine group compared with the placebo group (-56 mg vs -8 mg, P = 0.037). Median differences were similar for high dose and low dose. The 7-day cumulative lorazepam requirements were not statistically different. Rates of agitation were similar across all groups.[22]

In a single centre Italian trial, 72 patients were randomised to a dexmedetomidine infusion or placebo. Both groups received symptom triggered 10 mg boluses of diazepam. The primary efficacy outcomes were 24-h diazepam consumption and cumulative diazepam dose requirement. Median 24-h diazepam consumption during the study was significantly lower in the dexmedetomidine group (20 mg vs 40 mg, P < 0.001), as was median cumulative diazepam dose during the ICU stay (60 mg vs 90 mg, P < 0.001). The median (IQR) percentage of time in the target sedation range was higher in the dexmedetomidine group also {90% (90-95) vs 64.5 % (60-72.5); P < 0.001).[23]

Should we use baclofen for the prevention of agitation in critically ill, mechanically ventilated patients with unhealthy alcohol use?

No, although the BACLOREA trial reported less agitation with baclofen use, this did not translate into improved outcomes, with the resultant deeper sedation producing longer durations of mechanical ventilation and ICU admission.

References

1. Reade MC & Finfer S. Sedation and Delirium in the Intensive Care Unit. N Engl J Med 2014;370:444-454

2. Stewart D, Kinsella J, McPeake J, Quasim T & Puxty A. The influence of alcohol abuse on agitation, delirium and sedative requirements of patients admitted to a general intensive care unit. J Intensive Care Soc 2019;20(3):208-215

3. Cooney G, Heydtmann M & Smith ID. Baclofen and the Alcohol Withdrawal Syndrome-A Short Review. Front Psychiatry 2019;9:773

4. Awissi DK, Lebrun G, Coursin DB, Riker RR & Skrobik Y. Alcohol withdrawal and delirium tremens in the critically ill: a systematic review and commentary. Intensive Care Med 2013;39(1):16-30

5. National Clinical Guideline Centre (UK). Alcohol Use Disorders: Diagnosis and Clinical Management of Alcohol-Related Physical Complications [Internet]. London: Royal College of Physicians (UK); 2010.

6. Devlin JW, Skrobik Y, Gélinas C, Needham DM, Slooter AJC, Pandharipande PP et al. Clinical Practice Guidelines for the Prevention and Management of Pain, Agitation/Sedation, Delirium, Immobility, and Sleep Disruption in Adult Patients in the ICU. Crit Care Med 2018;46(9):e825-e873

7. de Beaurepaire R, Sinclair JMA, Heydtmann M, Addolorato G, Aubin HJ, Beraha EM et al. The Use of Baclofen as a Treatment for Alcohol Use Disorder: A Clinical Practice Perspective. Front Psychiatry 2019;9:708

8. DeCarolis DD, Rice KL, Ho L, Willenbring ML & Cassaro S. Symptom-driven lorazepam protocol for treatment of severe alcohol withdrawal delirium in the intensive care unit. Pharmacotherapy 2007;27(4):510-518

9. Spies CD, Otter HE, Hüske B, Sinha P, Neumann T, Rettig J et al. Alcohol withdrawal severity is decreased by symptom-orientated adjusted bolus therapy in the ICU. Intensive Care Med 2003;29(12):2230-2238

10. Brotherton AL, Hamilton EP, Kloss HG & Hammond DA. Propofol for treatment of refractory alcohol withdrawal syndrome: a review of the literature. Pharmacotherapy 2016;36(4):433-442.

11. Mueller SW, Preslaski CR, Kiser TH, Fish DN, Lavelle JC, Malkoski SP et al. A randomized, double-blind, placebo-controlled dose range study of dexmedetomidine as adjunctive therapy for alcohol withdrawal. Crit Care Med 2014;42(5):1131-1139

12. Agabio R, Sinclair JM, Addolorato G, Aubin HJ, Beraha EM, Caputo F et al. Baclofen for the treatment of alcohol use disorder: the Cagliari Statement. Lancet Psychiatry 2018;5(12):957-960

13. Vourc'h M, Dailly E, Hourmant Y, Bellouard R, Mahe PJ, Deslandes G et al. Pharmacokinetics and toxicity of high-dose baclofen in ICU patients. Prog Neuropsychopharmacol Biol Psychiatry 2019;92:450-456

14. Ewing JA. Detecting alcoholism. The CAGE questionnaire. JAMA 1984;252:1905–1907

15. Huai J & Ye X. A meta-analysis of critically ill patients reveals several potential risk factors for delirium. Gen Hosp Psychiatry 2014;36:488–496

16. Lyon JE, Khan RA, Gessert CE, Larson PM & Renier CM. Treating alcohol withdrawal with oral baclofen: a randomized, double-blind, placebo-controlled trial. J Hosp Med 2011;6(8):469-74

17. Girish K, Vikram Reddy K, Pandit LV, Pundarikaksha HP, Vijendra R, Vasundara K et al. A randomized, open-label, standard controlled, parallel group study of efficacy and safety of baclofen, and chlordiazepoxide in uncomplicated alcohol withdrawal syndrome. Biomed J 2016;39(1):72-80

18. Addolorato G, Leggio L, Abenavoli L, Agabio R, Caputo F, Capristo E, et al. Baclofen in the treatment of alcohol withdrawal syndrome: a comparative study vs diazepam. Am J Med 2006;119(3):276:e13-8

19. Spies CD, Dubisz N, Neumann T, Blum S, Muller C, Rommelspacher H et al. Therapy of alcohol withdrawal syndrome in intensive care unit patients following trauma: results of a prospective, randomised trial. Crit Care Med 1996;24:414–422

20. Spies CD, Otter HE, Huske B, Sinha P, Neumann T, Rettig J et al. Alcohol withdrawal severity is decreased by symptom-orientated adjusted bolus therapy in the ICU. Intensive Care Med 2003;29:2230–2238

21. Elsing C, Stremmel W, Grenda U, & Herrmann T. Gammahydroxybutyric acid versus clomethiazole for the treatment of alcohol withdrawal syndrome in a medical intensive care unit: an open, single-center randomized study. Am J Drug Alcohol Abuse 2009;35:189–192

22. Mueller SW, Preslaski CR, Kiser TH, et al. A randomized, double-blind, placebo-controlled dose range study of dexmedetomidine as adjunctive therapy for alcohol withdrawal. Crit Care Med 2014;42(5):1131-1139

23. Bielka K, Kuchyn I, & Glumcher F. Addition of dexmedetomidine to benzodiazepines for patients with alcohol withdrawal syndrome in the intensive care unit: a randomized controlled study. Ann Intensive Care 2015;5(1):33

MENDS2

Hughes CG, Mailloux PT, Devlin JW, Swan JT, Sanders RD, Anzueto A, et al. Dexmedetomidine or Propofol for Sedation in Mechanically Ventilated Adults with Sepsis. N Engl J Med 2021; 384:1424-1436

Introduction

Sedation is frequently used in critical care for patient comfort and safety. A minority of patients have an indication for continuous deep sedation, with most patients requiring only light sedation with the goal they are calm, lucid, pain-free, interactive, and cooperative with their care. Minimising sedation reduces time receiving mechanical ventilation and the duration spent in the ICU.[1] Whilst there is consensus on the depth of sedation, the choice of primary sedative agent less certain.[2]

Guidelines recommend using opioid drugs for analgesia as first-line therapy, introducing the short-acting GABA-agonist propofol for sedation, avoiding benzodiazepines, and suggest dexmedetomidine as an alternative agent.[2] This is largely reflected in real world practice, with propofol being the most commonly used agent, with intermittent use of dexmedetomidine.[3] Propofol allows rapid awakening but can accumulate with longer term use and has been known to cause propofol infusion syndrome.[4]

Dexmedetomidine a sedative with predominantly α2-adrenoreceptor affinity, has been extensively investigated in critical care, and may have advantages over more traditionally used sedatives, as it additionally provides analgesia and potentially causes less respiratory depression. When compared to the benzodiazepines, lorazepam and midazolam, dexmedetomidine resulted in less delirium and a shorter duration of mechanical ventilation.[5,6] In comparison to propofol, results were comparable, although dexmedetomidine sedated patients were reported to be more interactive.[7] Furthermore, when added to standard care in agitated patients, dexmedetomidine treated patients were able to be extubated earlier.[8] However, these apparent advantages were not replicated in the largest randomised trial to date, when dexmedetomidine was compared to usual care in a mixed intensive care population.[9] In fact, this trial showed additional sedatives were often required to supplement dexmedetomidine sedation. In selected patients with sepsis, dexmedetomidine may still have a specific rationale for use, with some trials reporting lower mortality rates.[5,10] These findings have a biological rationale, with dexmedetomidine having anti-inflammatory and immunomodulatory effects.[11,12]

With these potential beneficial and plausible effects, the MENDS2 trial was designed to investigate if septic patients would benefit from dexmedetomidine sedation.

Synopsis

This multi-center, double blinded, randomised trial, performed in 13 ICUs in the United States, compared the use of propofol with dexmedetomidine for sedation of critically ill patients with sepsis. Adult patients with suspected infection requiring sedation for invasive mechanical ventilation within 96 hours of admission were eligible for recruitment. Patients were excluded if they had baseline severe cognitive impairment, had language difficulties or were blind or deaf. Additionally, trial drug allergy, a specific indication for treatment with benzodiazepines, 2nd or 3rd degree heart block or patients with bradycardia requiring treatment, pregnant patients and breastfeeding patients, were also excluded. Patients deemed suitable for extubation, or conversely were felt to require neuromuscular blockade for >48hrs, were also not recruited.

Participants were enrolled and randomly allocated in a 1:1 ratio to receive sedation with propofol or dexmedetomidine. This occurred via a central computer-generated sequence, stratified by trial site and age (<65 vs >65yrs). A trial pharmacist prepared the trial drugs (dexmedetomidine 5 µg/mL & propofol 10 mg/mL) in identical fluid bags. Both the bags and intravenous tubing were covered. The blinded trial drug infusions were commenced at an equivalent rate to the pre-randomisation sedation infusion. Subsequently, the unblinded bedside nurse titrated the infusion to sedation goals decided by the clinical team. Sedation goals were set using the Richmond Agitation Sedation Scale (RASS). Infusion rates were 0.15 to 1.5 µg/kg of actual body weight per hour for dexmedetomidine and 5 to 50 µg/kg of actual body weight per minute for propofol. The trial sedation was continued for up to 14 days or until extubation. If a patient required reintubation within this time the trial drug was recommenced. Patients were allowed analgesia with fentanyl infusion or opioid boluses. Trial sedation was held for hypotension, bradycardia, over sedation, awakening trials or need for an operative procedure. If a patient developed symptomatic bradycardia or heart block, the trial drug was permanently discontinued. The ABCDE (awakening and breathing coordination, choice of sedation, delirium monitoring and management, and early mobility) bundle was recommended and adherence recorded. All other clinical management was at the discretion of the treating physician. Research personnel recorded RASS, Confusion Assessment Method for the ICU (CAM-ICU), and the Critical Care Pain Observation Tool, twice daily in the ICU and then once daily thereafter for up to 14 days or until discharge or death. A RASS score of −4 or −5 indicated coma, and a positive CAM-ICU score indicated delirium. Six months after randomization, patients were assessed for cognitive and functional status and quality of life via telephone interview.

The primary outcome was the number of calendar days alive without delirium or coma during the 14-day intervention period. Secondary outcomes included ventilator-free days

at 28 days, death at 90 days, and global cognition at 6 months using the age-adjusted TICS total score (Telephone Interview for Cognitive Status, TICS-T score).

After a protocol amendment, due to slow recruitment, the initial target of 530 patients was reduced to 420 patients. This would provide 85% power to detect a 1.5 day difference in days alive without delirium or coma, and 80% power to detect a 12% absolute difference in mortality at 90 days assuming a 30% mortality in the Propofol group, and 80% power to detect a 3.9 point difference in TICS-T scores between groups. Data was analysed in a modified intention to treat population for patients who were randomised and received trial drug.

Over a five-year period, 4840 patients were screened and 4402 met exclusion criteria. Of those excluded, 911 patients were ventilated for > 96 hours, 771 had severe cognitive impairment, 1008 declined consent and 563 had a requirement for benzodiazapines. A total of 432 patients were randomised, and after further exclusions, 214 were allocated to the dexmedetomidine group and 208 to the propofol group.

Baseline characteristics were similar in the two groups; patients were around sixty years of age, approximately 57% of patients were male and predominantly of white ethnic origin (87%). The median SOFA score was 10, with 52% of patients requiring vasopressor support; lung and blood stream the main sources of infection. Patients were recruited a median of 1 day after ICU admission with around 61% of patients receiving pre-randomization propofol, 32% receiving benzodiazepines and 14% dexmedetomidine.

During the trial intervention period, the median RASS score was −2 (IQR, −3.00 to −1.00). Patients received the trial drug for a median 3.0 days (IQR, 2.0 to 6.0). The overall time spent at target sedation was close to 60% in both groups. The trial drug was temporarily held in approximately one quarter of all patients. Rescue midazolam was used in about half of patients, most often for procedural sedation or during neuromuscular blockade, and the median daily exposure, on days it was administered, was 4 mg (interquartile range, 2 to 11). Open label propofol was required in 13% of the dexmedetomidine group and 8% in the propofol group. 42% of patients received antipsychotic medications and 96% had soft wrist restraints.

There was no significant difference in the primary outcome measure of days alive without delirium or coma over the 14-day period, between the dexmedetomidine group (adjusted median, 10.7 days; 95% CI, 8.5 to 12.5) and the propofol group (adjusted median, 10.8 days; 95% CI, 8.7 to 12.6) (odds ratio, 0.96; 95% CI, 0.74 to 1.26; P=0.79).

Secondary outcomes were consistent with the primary outcome. There were no significant differences between the dexmedetomidine and propofol groups in the number of ventilator-free days at 28 days (adjusted median, 23.7 vs. 24.0 days; odds ratio, 0.98; 95% CI, 0.63 to 1.51) or in death at 90 days (38% vs 39%; HR, 1.06; 95% CI, 0.74 to 1.52). At six month follow up, there were no differences in the cognitive assessment scores, functional outcome or quality of life, although around one quarter of patients had a cognitive score two standard deviations below normal.

Again, safety outcomes were similar between groups. There were no differences in patients experiencing organ dysfunction, hypotension or bradycardia. However, more patients in the dexmedetomidine group self extubated.

Critique

Delirium is a common problem in the critically ill and is associated with increased mortality and poorer long-term functional and cognitive outcomes.[13] It is a complex condition, compounded by a limited understanding of its pathophysiology. Of the multiple risk factors, including age, coma, neurological diagnosis, sedative medications, and severity of illness, sepsis is particularly important.[13] The realisation that sedation can exacerbate delirium and worsen outcomes has led to numerous trials comparing sedative regimens.[13]

Dexmedetomidine, in comparison to benzodiazepines, was shown to have better outcomes, particularly in septic patients.[5,6] Benzodiazepines have been independently associated with delirium and are no longer recommended as first line sedative agents.[2,3,13] In the SPICE III trial focusing on light sedation, when compared to propofol sedation, dexmedetomidine sedation had no effect on mortality in either septic or non-septic patients. This finding was limited by considerable exposure to non-trial sedatives.[9] Despite this, in the SPICE III trial, days free from delirium and coma were a day longer in the dexmedetomidine group. With further plausible anti-inflammatory and anti-apoptosis effects (although the success of immune modulation in sepsis is poor), further examination of the use of dexmedetomidine in critically unwell patients with sepsis was justifiable.

Two-thirds of enrolled patients had infections confirmed by culture. This was the target population the trialists postulated would benefit most from dexmedetomidine sedation. Despite this high acuity of confirmed infections, only approximately 50% required vasopressors. It may have been those recruited were less unwell than anticipated to benefit from the theoretical immunological effects of this sedative, although the overall mortality rate still approached 40%.

This was a well conducted trial, with an impressive effort to ensure blinding, which is unusual for this type of trial. Although the sedative and infusion tubing were covered, the bedside nurse was not blinded. The protocol incorporated validated scales for the titration of sedation (RASS),[14] diagnosis of delirium (CAM-ICU)[15] and included the ABCDE (awakening and breathing coordination, choice of sedation, delirium monitoring and management, and early mobility) bundle,[16] with excellent adherence achieved. These measures helped ensure the trial interventions were delivered in a consistent and high-quality manner. Yet, perhaps the high adherence, in particular to the ABCDE bundle which has been shown to significantly reduce the incidence of coma, delirium and death, might also have minimised any benefit dexmedetomidine may have over profofol.[17]

Evidence from randomized, controlled trials consistently supports the use of the minimum possible level of sedation. The mean RASS score was -2 in both groups suggesting light sedation was achieved.[13] The combined effect of these good practice interventions would be to maximise the primary outcome measure in both groups. The trial aimed to achieve a 1.5 day difference in days alive without delirium or coma over only fourteen days, which was half the time in the SPICE 3 trial. It was also hampered by poor recruitment, such that trial enrolment target was reduced, potentially resulting in the trial being underpowered to detect the intended treatment effect.

A further challenge of conducting sedation trials is cross-contamination of sedatives. In the MENDS-2 trial, patients were commenced on the trial sedative a median of 22 hours after meeting inclusion criteria. In this preceding period, the dexmedetomidine group had been exposed to propofol (61%), benzodiazepines (29%) and antipsychotics (11%) prior to commencement of the trial drug. In addition, almost 50% of patients at this stage were deeply sedated. This prior exposure may have nullified any beneficial effects. SPICE 3, a trial which showed reduced delirium when patients were recruited within 5 hours, limited time exposure to other medications. Post recruitment, there was also significant exposure to benzodiazepines (53%) and also antipsychotics (42%). This does perhaps reflect the findings of SPICE 3 trial which suggested additional sedatives were required with dexmedetomidine sedation. Interestingly, there were high rates of use of benzodiazepines (43%) and also antipsychotics (42%) in the propofol group.[9] The use of benzodiazepines, which are associated with delirium, seems counterproductive to the trial aims. The usage was much higher in the MENDS-2 trial that SPICE 3, and may account for the difference in the trial in terms of delirium free days.[9] The MENDS-2 trial did manage to limit the post randomisation use of propofol in the dexmedetomidine group (much lower than SPICE 3) but perhaps a better approach would have been to use short acting propofol as required for deeper sedation, in order to avoid “deliriogenic” medications. The addition of dexmedetomidine to usual care has been shown to reduce delirium, when benzodiazepine use is low.[8]

Perhaps the high requirement for other sedative medication in the trial, despite the achievement of light sedation, was due to the low dose of trial drug used in each group. The median dose of propofol was 10 µg/kg/min (about 40 mg/hr in an average adult) versus 0.27 µg/kg/hr dexmedetomidine, which is the lowest recommended dosing regimen. These doses were lower than in the SPICE 3 trial or the DahLIA trial both of which showed beneficial effects of dexmedetomidine.[8,9]

Sedation guidelines recommend analgesia and then sedative medications.[2] Fentanyl appeared to be used both as an analgesic and a sedative, with a resulting high median dose being delivered, the equivalent of around 140 mg of morphine per day. In contrast, a recent trial of no or minimal sedation successfully managed pain with around 10 mg of morphine per day.[18] The large difference in analgesic requirements between the two populations is difficult to explain, but leaves the MENDS-2 trial as a high dose opioid trial with low dose sedative infusions and other sedatives as required. It is perhaps not unsurprising there was little separation between the two groups in either primary or secondary outcomes.

Where this sits in the body of evidence

In a double-blind, two-centre, randomised controlled trial, 106 ventilated adults were randomised to either sedation with dexmedetomidine or lorazepam. The primary outcome was days alive without delirium or coma and days spent at RASS range. Sedation with dexmedetomidine resulted in more days alive without delirium or coma (7.0 vs 3.0; P = 0.01), and a lower prevalence of coma (63% vs 92%; P < 0.001), than sedation with lorazepam. Mortality was also lower in the dexmedetomidine group.[5]

In a prospective, double-blind, randomised trial conducted in 68 centres in 5 countries, 375 adult patients expected to require more than 24 hrs of ventilation were randomised to sedation with infusions of either dexmedetomidine or midazolam. The primary outcome was time within target RASS score. Secondary outcomes were incidence and duration of delirium, use of additional sedatives, as well as duration of ventilation and length of stay. There was no difference time in the target RASS range (77.3% for dexmedetomidine group vs 75.1% for midazolam group). The prevalence of delirium during treatment was 54% in dexmedetomidine-treated patients vs 76.6% in midazolam-treated patients (difference, 22.6%; 95% CI, 14% to 33%; P<0.001). Median time to extubation was 1.9 days shorter in dexmedetomidine-treated patients.[6]

Two paired phase three blinded randomised trials were reported together in a single publication in JAMA in 2012. The MIDEX trial compared midazolam with dexmedetomidine in 44 centers in 9 European countries. The PRODEX trial compared propofol with dexmedetomidine in 31 centers in 6 European countries and 2 centers in

Russia. Both trials included lightly sedated patients in the ICU receiving mechanical ventilation. Both trials examined whether dexmedetomidine was noninferior to midazolam/propofol with regard to the proportion of time at target sedation level and superior with regard to the duration of mechanical ventilation. 998 patients were included, roughly equally divided between all 4 groups; MIDEX: midazolam, n=251; dexmedetomidine, n=249; PRODEX: propofol, n=247; dexmedetomidine, n=251. The dexmedetomidine / midazolam ratio in time at target sedation was 1.07 (95% CI, 0.97 to 1.18) and dexmedetomidine/propofol, 1.00 (95% CI, 0.92 to 1.08). Median duration of mechanical ventilation appeared shorter with dexmedetomidine (123 hours; IQR, 67-337) vs midazolam (164 hours; IQR, 92-380; P = 0.03) but not with dexmedetomidine (97 hours IQR; 45-257) vs propofol (118 hours; IQR, 48-327; P = 0.24).[7]

The DahLIA trial from the ANZICS group was a double-blind, placebo-controlled, parallel-group randomised clinical trial evaluating dexmedetomidine in 74 adult patients in whom extubation was considered inappropriate because of the severity of agitation and delirium. Patients were randomised to dexmedetomidine or placebo for up to 7 days. The primary outcome was ventilator-free hours in the 7 days following randomisation. Dexmedetomidine increased ventilator-free hours at 7 days compared with placebo (median, 144.8 hours vs 127.5 hours, respectively; median difference between groups, 17.0 hours (95% CI, 4.0 to 33.2 hours; P = 0.01).[8]

SPICE III was a multi-centre, open-label, randomised control trial conducted in 74 ICUs across the world. 4000 adult patients within 12 hours of initiation of ventilation were randomised to sedation with dexmedetomidine alone or usual care. Target sedation using the RASS was -2 to +1. The primary outcome was 90-day mortality. Secondary outcomes included measures of cognitive, functional and quality of life. Overall there was no difference in 90-day mortality, 29.1% in the dexmedetomidine group versus 29.1% in the usual care group (adjusted risk difference, 0.0%; 95% CI, −2.9 to 2.8). Despite the target sedation being early light sedation, clinicians chose deep sedation for 50-60% of patients on days 1-2. More than 60% of patients in the dexmedetomidine group received additional sedatives, mainly propofol. In a sub group analysis, there was a possible difference in mortality for patients above and below the median patient age.[9]

In an unblinded multi-centre trial in 8 ICUs in Japan, 201 adult patients with sepsis were randomised to sedation with dexmedetomidine (n = 100) or sedation without dexmedetomidine (control group; n = 101). Other agents were used in addition. The primary outcomes were mortality and ventilator-free days at 28 days. Mortality at 28 days was not significantly different in the dexmedetomidine group vs the control group (22.8% vs 30.8%; HR, 0.69; 95% CI, 0.38 to 1.22; P = 0.20). Ventilator-free days over 28 days were not significantly different between groups {dexmedetomidine group, median

20 (5-24) days; control group: median 18 (0.5-23) days; P = 0.20}. No other outcomes were significantly different between groups.[10]

Should we preferentially use dexmedetomidine sedation, in preference to propofol, in critically ill patients with sepsis requiring mechanical ventilation

No, the data from the MENDS trial adds to the evidence base suggesting overall similar outcomes between these agents when used in the ICU.

References

1. Kress JP, Pohlman AS, O'Connor MF & Hall JB. Daily interruption of sedative infusions in critically ill patients undergoing mechanical ventilation. N Engl J Med 2000;342:1471-1477

2. Devlin JW, Skrobik Y, Gélinas C, Needham DM, Slooter AJC, Pandharipande PP, et al. Clinical practice guidelines for the prevention and management of pain, agitation/sedation, delirium, immobility, and sleep disruption in adult patients in the ICU. Crit Care Med 2018;46:e825–73

3. Richards-Belle A, Canter RR, Power GS, Robinson EJ, Reschreiter H, Wunschet H et al. National survey and point prevalence study of sedation practice in UK critical care. Crit Care 2016;20(1):355

4. Shehabi Y, Bellomo R, Mehta S, Riker R & Takala J. Intensive care sedation: the past, present and the future. Crit Care 2013;17:322

5. Pandharipande PP, Pun BT, Herr DL, Maze M, Girard TD, Miller RR et al. Effect of sedation with dexmedetomidine vs lorazepam on acute brain dysfunction in mechanically ventilated patients: the MENDS randomized controlled trial. JAMA 2007;298:2644-2653

6. Riker RR, Shehabi Y, Bokesch PM, Ceraso D, Wisemandle W, Koura F et al. Dexmedetomidine vs midazolam for sedation of critically ill patients: a randomized trial. JAMA 2009;301:489-499

7. Jakob SM, Ruokonen E, Grounds RM, Sarapohja T, Garratt C, Pocock SJ et al. Dexmedetomidine vs midazolam or propofol for sedation during prolonged

mechanical ventilation: two randomized controlled trials. JAMA 2012;307:1151-1160

8. Reade MC, Eastwood GM, Bellomo R, Bailey M, Bersten A, Cheung B et al. DahLIA Investigators; Australian and New Zealand Intensive Care Society Clinical Trials Group. Effect of Dexmedetomidine Added to Standard Care on Ventilator-Free Time in Patients With Agitated Delirium: A Randomized Clinical Trial. JAMA 2016;315(14):1460-8.

9. Shehabi Y, Howe BD, Bellomo R, Arabi YM, Bailey M, Bass FE et al; ANZICS Clinical Trials Group and the SPICE III Investigators. Early Sedation with Dexmedetomidine in Critically Ill Patients. N Engl J Med 2019;380(26):2506-2517.

10. Kawazoe Y, Miyamoto K, Morimoto T, Yamamoto T, Fuke A, Hashimoto A,et al. Dexmedetomidine for Sepsis in Intensive Care Unit Randomized Evaluation (DESIRE) Trial Investigators. Effect of Dexmedetomidine on Mortality and Ventilator-Free Days in Patients Requiring Mechanical Ventilation With Sepsis: A Randomized Clinical Trial. JAMA 2017;317(13):1321-1328

11. Ueki M, Kawasaki T, Habe K, Hamada K, Kawasaki C, Sata T. The effects of dexmedetomidine on inflammatory mediators after cardiopulmonary bypass. Anaesthesia 2014;69:693-700

12. Si YN, Bao HG, Xu L, Wang XL, Shen Y, Wang JS, et al. Dexmedetomidine protects against ischemia/reperfusion injury in rat kidney. Eur Rev Med Pharmacol Sci. 2014;18(13):1843-51

13. Reade MC & Finfer S. Sedation and Delirium in the Intensive Care Unit. N Engl J Med 2014;370:444-454

14. Sessler CN, Gosnell MS, Grap MJ, Brophy GM, O'Neal PV, Keane KA et al. The Richmond Agitation-Sedation Scale: validity and reliability in adult intensive care unit patients. Am J Respir Crit Care Med 2002;166(10):1338-44

15. Ely EW, Inouye SK, Bernard GR, Gordon S, Francis J, May L, et al.. Delirium in mechanically ventilated patients: validity and reliability of the confusion assessment method for the intensive care unit (CAM-ICU). JAMA 2001;286(21):2703-10

16. Barnes-Daly MA, Phillips G, Ely EW. Improving hospital survival and reducing brain dysfunction at seven California community hospitals: implementing PAD guidelines via the ABCDEF bundle in 6,064 patients. Crit Care Med 2017;45:171-178

17. 17 Pun BT, Balas MC, Barnes-Daly MA, Thompson JL, Aldrich JM, Barr J et al. Caring for Critically Ill Patients with the ABCDEF Bundle: Results of the ICU Liberation Collaborative in Over 15,000 Adults. Crit Care Med 2019;47(1):3-14

18. 18 Olsen HT, Nedergaard HK, Strøm T, Oxlund J, Wian K, Ytrebø LM et al. Nonsedation or Light Sedation in Critically Ill, Mechanically Ventilated Patients. N Engl J Med 2020;382:1103-1111

COBI

Roquilly A, Moyer JD, Huet O, Lasocki S, Cohen B, Dahyot-Fizelier C, et al. Effect of Continuous Infusion of Hypertonic Saline vs Standard Care on 6-Month Neurological Outcomes in Patients With Traumatic Brain Injury The COBI Randomized Clinical Trial. JAMA 2021;325(20):2056-2066

Introduction

Traumatic brain injury (TBI) affects around 70 million people globally every year, with nearly 33% of patients with TBI dying in hospital and another 33% having poor neurological recovery resulting in moderate to severe disability.[1,2] Guidelines for the management of TBI recommend physiological stabilisation with careful management of the airway, oxygenation and haemodynamic support to prevent secondary brain injury.[3] Subsequently, the mainstay of critical care management is cerebral monitoring using intracranial pressure (ICP) measurement. Patients with elevated ICP have been shown to have worse outcomes and are at a higher risk of mortality. As a result, prevention and treatment of intracranial hypertension (ICH) are priorities in the management of severe TBI, with the Brain Trauma Foundation recommending ICP is maintained ≤ 22 mm Hg.[3,4]

Management of raised ICP includes standardized strategies that use a "stepped approach". An escalating treatment schedule includes sedation, head positioning, optimisation of ventilation, followed by boluses of hyperosmolar therapy.[5] The most commonly used interventions are mannitol and hypertonic saline solutions. Although these solutions clearly have an effect on ICP, despite their widespread use, neither mannitol nor hypertonic saline have been proven to improve long-term outcomes.[3] Furthermore, questions remain as to whether mannitol or hypertonic saline has superior efficacy. A recent meta-analysis reported no significant difference between hypertonic saline and mannitol in terms of mortality or neurological outcome.[6] The dose, timing and method of administration of osmotic agents varied considerably. Bolus therapy is common but has been criticised due to the potential for subsequent rebound in ICP.[7] Continuous infusion of hyperosmolar therapy has, therefore, been proposed for the treatment of patients with severe brain injury. Sustained continuous hypertonic solution may increase blood osmolarity and subsequently prevent intracranial hypertension. Continuous therapy can decrease the risk of intracranial hypertension.[8] However, continuous infusions are currently not recommended due to a lack of high-quality evidence.[3] The COBI trial seeks to fill this important gap in the traumatic brain injury literature.

Synopsis

This multi-centre, open label, randomised trial performed in 9 ICUs in France compared the use of a continuous infusion of 20% hypertonic saline solution plus standard care or standard care alone in TBI patients. Adult patients admitted within twenty-four hours of a moderate to severe TBI were eligible for randomization. Moderate to severe TBI was defined as a Glasgow Coma Scale (GCS) score of 12 or lower, with an abnormal computed tomography (CT) brain scan (extradural hematoma, subdural hematoma, subarachnoid haemorrhage, brain contusion, brain hematoma, brain oedema, or skull fracture). Patients were excluded if they had suffered a cervical spinal cord injury, had a GCS of 3 with fixed dilated pupils, had premorbid dependency or had fluid retention (considered a contraindication to sodium administration). Pregnant patients were also excluded.

Patients were randomised in a 1:1 ratio, in fixed blocks of 6, using a web-based system with stratification based on the GCS score (3-8 vs 9-12), and on whether the patient had been administered a bolus of hyperosmolar therapy before inclusion in the study. Those randomised to the continuous infusion group received a bolus infusion of 20% hypertonic saline over 1 hour (dose adapted to the basal blood level of sodium) immediately after randomisation, followed by a continuous infusion (0.5-1 g/h of NaCl) and adapted to the patients' serum sodium levels to limit the risk of severe hypernatremia (defined as Na^+ >155 mmol/L). The intervention was continued for at least 48 hours and stopped when all specific therapies for ICH were discontinued for more than 12 hours. Sodium levels were monitored every 8 hours during the intervention and for the following 48 hours. If serum sodium dropped below 140 mmol/L, or decreased more than 12 mmol/L per day, then further boluses of hypertonic saline was administered. Standard therapy conformed to the revised Brain Trauma Foundation guidelines. Isotonic crystalloid solutions were used as maintenance fluids and first-line resuscitation fluids. Intracranial hypertension was treated as per guidelines, including boluses of sedative drugs and hyperosmolar therapy (200-250 mOsm of mannitol or hypertonic saline), moderate hypothermia, cerebrospinal fluid drainage, ventilation therapy, or decompressive craniectomy.

The primary outcome was the Extended Glasgow Outcome Scale (GOS-E) score at 6 months. Follow up interviews were performed by researchers blinded to the intervention allocation. Secondary outcomes were mortality at 6 months; GOS-E score at 3 months; duration of posttraumatic amnesia evaluated at ICU discharge, 3 months, and 6 months; autonomy in activities of daily living at 3 and 6 months (Katz Index of Independence in Activities of Daily Living >6); quality of life, estimated by the Short Form 36 health survey at 3 months and 6 months (self- questionnaire); and place of residence at 3 months and 6 months.

Changes in serum sodium, chloride, potassium, creatinine and pH levels, as well as blood osmolarity were recorded every 8 hours during treatment. Intracranial pressure was also recorded. The intensity of the management of ICH was estimated by the frequency of episodes of ICH (pressure >22 mm Hg for more than 20 minutes), the frequencies and durations of hyperosmolar therapy, therapeutic hypothermia, barbiturate coma, moderate hypocapnia, external ventricular drainage, and the frequency of decompressive craniectomy. Safety outcomes included the frequency of kidney failure, severe thromboembolic events and the incidence of centropontine myelinolysis.

Based on a reported incidence of 70% rate of poor neurological outcome in the control group and of 56% in the intervention group, 370 patients (185 patients per group) were required to detect a relative decrease of 20% with 80% power and a two-side alpha of 0.05%. Patients were analysed according to their randomization group. The primary outcome measure (GOS-E score at 6 months) was analysed with an ordinal method based on the proportional odds model. The proportional odds model was adjusted for key baseline covariates (age, GCS score, pupillary reactivity, hypotension, hypoxia, and brain CT classification), covariates used for stratification at randomisation (trauma severity and administration of a bolus of hyperosmolar therapy before inclusion), and centres.

Over a 3-year period, 393 patients were screened, 23 were excluded, and 370 patients were randomised, 185 to each group. Subsequently, 8 patients were lost to follow up. Of the 370 patients, 293 (79.1%) were men, the median age was around 45 years and approximately 71.6% of patients had a GCS < 8. Patient baseline characteristics at randomization were largely similar, although the intervention group had more grade III and IV diffuse brain injury on Marshall CT brain classification (17.4% vs. 12.6%), more evacuable mass lesions (25% vs. 14.8%) and higher incidence of neurosurgical intervention (32.1 vs. 22.0%) prior to randomisation than the control arm.

Continuous infusion of 20% hypertonic saline solution was administered for a mean (SD) of 2.7 (1.3) days in the intervention group. No patient in the control group received this treatment as rescue therapy. The intervention was significantly associated with higher blood osmolarity and sodium concentration. The intervention was also significantly associated with a reduction of the risk of intracranial hypertension (OR, 0.07; 95% CI, 0.02 to 0.20). There was a significant interaction between the treatment effect and time (OR, 2.50; 95% CI, 1.89 to 3.29) suggesting a rebound of ICH risk after intervention discontinuation.

For the primary outcome, the test of the proportional odds assumption showed no significant difference in the 6-month GOS-E score distribution between the 2 groups (P = 0.08). Furthermore, the distribution of GOS-E scores was not significantly shifted in the

intervention group in comparison with the control group (adjusted common OR, 1.02; 95% CI, 0.71 to 1.47; P = 0.92).

In terms of the secondary outcomes, ICH episodes occurred in 62 patients (33.7%) in the intervention group and 66 patients (36.3%) in the control group (absolute difference, −2.6%; 95% CI, −12.3% to 7.2%; adjusted OR, 0.80; 95% CI, 0.51 to 1.26). Moderate hypocapnia was induced in 11.5% of the patients in the intervention group and 5.5% in the control group (difference, 6.1%; 95% CI, 0.3% to 11.9%). The rates and durations of the other interventions were not significantly different between the study groups.

Favourable neurological outcomes at 6 months occurred in 59 of 181 patients (32.6%) in the intervention group and 63 of 178 patients (35.4%) in the control group (absolute difference, −2.8%; 95% CI, −12.6% to 7.0%; adjusted OR, 0.85; 95% CI, 0.53 to 1.36). There was no significant difference in 6-month mortality (15.9%) in the intervention group vs (20.8%) in the control group; absolute difference, −4.9%; 95% CI, −12.8% to 3.1%; HR, 0.79; 95% CI, 0.48 to 1.28). There were no differences in measures of disability or quality of life at six months.

Adverse event rates were similar between groups, at 27% in the intervention group and 24.9% in the control group. The rates of severe hypernatremia (sodium level >160 mmol/L) were 12.4% in the intervention group and 6% in the control group. Thromboembolic events were recorded in 6% intervention and 2.2% control group.

Critique

Despite guideline recommendations and routine clinical use of osmotherapy to treat raised ICP, neither mannitol or hypertonic saline have been proved to improve long-term outcomes after TBI.[3,6] Direct comparative trials have failed to show a difference in neurological outcome measures, although hypertonic saline may have a more favourable onset of action.[9] However, the quality of the evidence is poor, with inconsistency in concentrations, volumes and method of administration, and differences in timing of doses. Nevertheless, hypertonic saline is increasingly used in critical care.[10] Hypertonic saline works by promoting the flux of water across the blood brain barrier and also improves blood flow by expanding the plasma volume. It has been used both as a bolus therapy and by continuous infusion.[11] Continuous infusions may offer more stable management of ICP by maintaining a stable serum sodium and plasma osmolality and has, therefore, been used both prophylactically and as treatment for raised ICP.[8,12,13,14] Despite a systemic review concluding that the use of continuous hypertonic saline infusion was associated with improved mortality and better neurological outcomes, the level of evidence is poor. Hence, the COBI trial was a timely and considered intervention in an area requiring further research.

The COBI trial ultimately did not show a difference in the primary outcome of GOSE at 6 months. The trial is the largest randomised trial investigating a continuous infusion of hypertonic saline. It was well conducted with all patients receiving the intervention, minimal withdrawals and an impressive rate of follow up of patients at six months. Although the intervention was not blinded, the neurological follow up assessors were not aware of the trial intervention.

The trial used a prophylactic infusion of hypertonic saline, in patients with moderate to severe TBI, to prevent ICH. This had a reasonable rationale as earlier intervention in patients with raised ICP had been associated with better outcomes and a small randomised trial had shown that prophylactically hypertonic saline had reduced episodes of raised ICP.[8,13] However, early prophylactic intervention risks recruiting patients who would not progress to the development of ICH, the population that was suggested would benefit. The trial included patients with moderate to severe TBI, defined as the association of a GCS ≤ 12 together with a traumatic abnormal brain CT scan. As few as 50% of these patients would develop raised ICP.[13] In the COBI trial, the control group experienced ICH in only 36.3% of patients. Hypertonic saline may have additional benefits beyond control of ICP, such as enhanced cardiac output and cerebral perfusion, counteracting vasospasm, and potentially limit glutamate-mediated neurotoxicity, which causes neuronal death.[15] Perhaps limiting the trial to patients with severe TBI might have selected a population of patients more like to respond to the intervention. Given that the trial was based on a hypothesised relative reduction of 20% in the rate of poor neurological outcome, which seems ambitious, then perhaps the trial was under powered to detect a difference in the clinical outcomes.

A further consideration in the trial size and recruitment was the variety of traumatic injuries sustained. The intervention group was both older (46 vs 43) and had a higher incidence of Grade III and IV diffuse brain injury on Marshall CT brain classification (17.4% vs. 12.6%), factors which are associated with worse outcomes.[16] This group also had more evacuable mass lesions (25% vs. 14.8%) and thus a greater incidence of neurosurgical intervention (32.1 vs. 22.0%) prior to randomisation. ICP monitoring after primary decompression is controversial, although this maybe a population with a higher risk of elevations in intracranial pressure.[17] Conversely, the control group had more non-evacuated mass lesions (20.9% vs 11.4%) which may have adverse prognostic implications.[16] Overall, these group differences make the interpretation of the results in the trial more difficult. Again, if either a larger population, or more specific population, had been recruited, the results might have provided more clarification as to the role of the intervention.

A surprising finding in the COBI trial was the apparent lack of effect the intervention had on the requirement for treatment interventions for raised ICP. Intracranial hypertension episodes occurred in 62 patients (33.7%) in the intervention group and 66 patients (36.3%) in the control group. Physiologically, the hypertonic saline group did have a separation in osmolarity and in sodium levels. Despite a bolus, this separation did not occur until around 8 hours after the intervention was commenced. This was in addition to a 12 to 13 hour period from injury until recruitment. An earlier intervention or larger bolus might have enhanced the separation, although earlier pre-hospital intervention with hypertonic saline may not produce an outcome benefit.[18] Interestingly, the serum sodium and plasma osmolarity in both groups were already above 140 mmol/L and over 300 mmol/L, respectively, at baseline, possibly reflecting the prior administration of hypertonic saline before randomisation in 55% of patients. The intervention did seem to have an effect on the ICP, with patients receiving hypertonic saline having less interventions in the first 48 hours. This was replaced with more interventions later, suggesting a rebound effect after the hypertonic saline was discontinued.

The serum sodium was monitored after the infusion was stopped, with intervention occurring if this value dropped below 140 mmol/L, or more than 12 mmol/day. It is somewhat surprising more stringent monitoring was not mandated. Finally, despite the difference in timing of interventions, the cerebral pressure data suggests good control of ICP was achieved and perfusion optimised as per current guidelines.[3] Perhaps this control is more important than the method of interventions to achieve it.

Where this sits in the body of evidence

In a double-blind, randomised controlled trial including 60 patients with severe TBI requiring ICP monitoring, a 48 hour continuous infusion of half-molar sodium lactate (0.5 ml/kg/h) was compared with an infusion of isotonic saline solution within the first 12 hours post-trauma. In the 48 hour study period, episodes of raised ICP were reduced in the intervention group as compared to the saline control group; 23 versus 53 episodes, respectively ($P < 0.05$). The proportion of patients with raised ICP episodes was smaller in the sodium lactate group than in the saline group, 36% versus 66% ($P < 0.05$). Cumulative 48 hour fluid and chloride balances were reduced in the intervention group compared to the control group (both $P < 0.01$).[8]

In a prospective, randomised control trial at two American teaching hospitals, 34 patients with severe trauma including TBI were randomised to fluid resuscitation with either hypertonic saline or lactated Ringer's solution. Those receiving hypertonic saline had a lower admission GCS (4.7±0.7 vs 6.7±0.7; P=0.057), a higher initial ICP (16±2 vs 11±2; P=0.06), and a higher initial mean maximum ICP (31±3 vs18±2; $P < 0.01$). Treatment effectively lowered ICP in both groups, with no significant difference between the

groups in ICP at any time. Patients receiving hypertonic saline required significantly more interventions (31±4; vs 11±3; P < 0.01).[12]

In a multi-centre prospective cohort trial, 1086 TBI patients with a GCS ≤ 12 and trauma-associated lesion on brain CT scan were studied. Of the 1086 patients, 545 patients developed ICH, 143 were treated with a continuous hypertonic saline infusion, while 402 received standard ICP management. The primary outcome was the risk of survival at 90 days. In patients with ICH, the relative risk of survival at day 90 with hypertonic saline was 1.43 (95% CI, 0.99 to 2.06, P = 0.05). At day 90, favourable outcomes (Glasgow Outcome Scale 4–5) occurred in 45.2% of treated patients with ICH and in 35.8% of patients with ICH not treated with hypertonic saline (P = 0.06). A review of the literature including 1304 patients from eight studies suggested that a continuous infusion of hypertonic saline is associated with a reduction of ICU mortality.[13]

In a single centre retrospective study, 50 patients with TBI and refractory ICH were treated with a continuous 20% saline infusion with a physician set sodium target. The infusion was initiated for a duration of approximately 7 days. ICP decreased from 29 (31±9) mm Hg to 20 (21±8) mm Hg at one hour (P < 0.05) with a subsequent rise in cerebral perfusion. No rebound of ICH was reported after stopping the continuous hypertonic saline infusion. Serum sodium increased from 140 to 144 mmol/L at 4 hours (P < 0.05). Plasma osmolarity increased from 275 mmol/L at time zero to 290 mmol/L at 24 hours (P < 0.05). There was no reported renal failure or pontine myelinolysis.[14]

In a single centre observational trial, 187 adult patients admitted to the neurosurgical ICU with a brain injury were treated with continuous 3% saline, at a rate of 1.5 mL/kg/bw as maintenance fluid, or with normal saline. Patients with TBI, stroke, or subarachnoid haemorrhage, and with a GCS < 9 and raised ICP or at risk of developing elevated ICP, were included. Treatment was at the discretion of the treating physician. A total of 53.3% in the hypertonic saline group and 16.3% in the 0.9% saline control group (p < 0.0001) had raised ICP (>25 mm Hg), consistent with the physicians decision to use hypertonic saline in patients with elevated ICP. The incidence of moderate hypernatremia (Na >155 mmol/L) and severe hypernatremia (Na >160 mmol/L) was significantly higher in the hypertonic saline group. There were no other adverse outcomes reported.[19]

Should we use continuous infusions of hypertonic saline in critically ill patients with moderate-to-severe traumatic brain injury?

No, the results of the COBI trial do not support the routine introduction of this intervention into neurocritical care practice.

References

1. Dewan MC, Rattani A, Gupta S, Baticulon RE, Hung YC, Punchaket M et al. Estimating the global incidence of traumatic brain injury. Journal of Neurosurgery 2019;130:1080–97

2. Myburgh JA, Cooper DJ, Finfer SR, Venkatesh B, Jones D, Higgins A, et al. Epidemiology and 12-month outcomes from traumatic brain injury in Australia and New Zealand. J Trauma. 2008;64:854-62

3. Carney N, Totten AM, O'Reilly C, Ullman JS, Hawryluk GWJ, Bell MJ et al. Guidelines for the management of severe traumatic brain injury, fourth edition. Neurosurgery 2017;80:6-15

4. Balestreri M, Czosnyka M, Hutchinson P, Steiner LA, Hiler M, Smielewski P et al. Impact of intracranial pressure and cerebral perfusion pressure on severe disability and mortality after head injury. Neurocrit Care 2006;4:8-13

5. Nathens AB, Cryer HG & Fildes J. The American college of surgeons trauma quality improvement program. Surg Clin North Am 2012;92:441-454

6. Schwimmbeck F, Voellger B, Chappell D & Eberhart L. Hypertonic saline versus mannitol for traumatic brain injury: a systematic review and meta-analysis with trial sequential analysis. J Neurosurg Anesth 2021;33:10-20

7. Francony G, Fauvage B, Falcon D, Canet C, Dilou H, Lavagne P et al. Equimolar doses of mannitol and hypertonic saline in the treatment of increased intracranial pressure. Crit Care Med 2008;36:795-800

8. Ichai C, Payen J-F, Orban J-C, Quintard H, Roth H, Legrand R et al. Half-molar sodium lactate infusion to prevent intracranial hypertensive episodes in severe traumatic brain injured patients: a randomized controlled trial. Intensive Care Med 2013;39(8):1413-1422

9. Cook, AM., Jones M, Hawryluk G, Mailloux G, McLaughlin P, Papangelou D et al. Guidelines for the Acute Treatment of Cerebral Edema in Neurocritical Care Patients. Neurocritical Care 2020;32(3):647-666

10. Hays AN, Lazaridis C, Neyens R, Nicholas J, Gay S & Chalela JA. Osmotherapy: use among neurointensivists. Neurocrit Care 2011;14(2):222-28

11. Dash HH & Chavali S. Management of traumatic brain injury patients. Korean J Anesthesiol 2018;71(1):12-21

12. Shackford SR, Bourguignon PR, Wald SL, Rogers FB, Osler TM & Clark DE. Hypertonic saline resuscitation of patients with head injury: a prospective, randomized clinical trial. J Trauma. 1998 Jan;44(1):50-8

13. Asehnoune K, Lasocki S, Seguin P, Geeraerts T, Perrigault PF, Dahyot-Fizelier C et al; ATLANREA Group; COBI Group. Association between continuous hyperosmolar therapy and survival in patients with traumatic brain injury—a multicentre prospective cohort study and systematic review. Crit Care. 2017;21(1):328

14. Roquilly A, Mahe PJ, Latte DDD, Loutrel O, Champin P, Di Falco C et al. Continuous controlled-infusion of hypertonic saline solution in traumatic brain-injured patients: a 9-year retrospective study. Crit Care 2011;15(5):R260

15. Tyagi R, Donaldson K, Loftus CM & Jallo J. Hypertonic saline: a clinical review. Neurosurg Rev 2007;30(4):277-289

16. Marshall LF, Marshall SB, Klauber MR, Van Berkum Clark M, Eisenberg H, Jane JA,et al. The diagnosis of head injury requires a classification based on computed axial tomography. J Neurotrauma 1992 Mar;9 Suppl 1:S287-92

17. Picetti, E., Caspani, M.L., Iaccarino, C. Pastorello G, Salsi P, Viaroli E et al. Intracranial pressure monitoring after primary decompressive craniectomy in traumatic brain injury: a clinical study. Acta Neurochir 2017;159:615–622

18. Cooper DJ, Myles PS, McDermott FT, Murray LJ, Laidlaw J, Cooper G et al. Prehospital hypertonic saline resuscitation of patients with hypotension and severe traumatic brain injury: a randomized controlled trial. JAMA 2004;291:1350-1357

19. Froelich M, Ni Q, Wess C, Ougorets I & Härtl R. Continuous hypertonic saline therapy and the occurrence of complications in neurocritically ill patients. Crit Care Med 2009;37(4):1433-41

Circulatory Trials

BaSICS – Fluid Rates

Zampieri FG, Machado FR, Biondi RS, Freitas FGR, Veiga VC, Figueiredo RC, et al. Effect of Slower vs Faster Intravenous Fluid Bolus Rates on Mortality in Critically Ill Patients. The BaSICS Randomized Clinical Trial. JAMA 2021;326(9):830-838

Introduction

Intravenous fluid administration is one of the most frequently performed interventions in critical care. In common with other widely-used interventions which are applied to large numbers of patients, even a small differential effect on mortality or other patient-centred outcomes has huge global health implications and is worth studying in an appropriately large clinical trial.

With growing awareness of the strong and consistent association between fluid accumulation or overload with adverse outcomes in critical illness, randomised trials of alternative fluid regimens have and are being undertaken. Perhaps the most striking of these was the FEAST trial comparing fluid boluses to restore perfusion with a gradual rehydration approach in children with hypoperfusion and infection, in Sub-Saharan Africa.[1] Contrary to expectations, FEAST showed that rapid infusion of fluid boluses resulted in higher mortality than a more gradual rehydration approach, despite similar overall volumes of fluid administration. Although these findings have not yet been replicated, a logical next question is whether rapid fluid administration can induce endothelial injury or another physiological insults, and whether these outweigh the proposed benefits of rapid restoration of perfusion in terms of patient outcomes.

No randomised studies have addressed this research question previously. Observational studies have provided some insights into current practice patterns, showing for example that 'typical' fluid boluses range from 250-500 mL over 15-30 minutes, with considerable variability in practice.[2] Overall, the trialists had very limited pilot data on which to base this trial.

Synopsis

The Balanced Solutions in Intensive Care Study (BaSICS) trial was an investigator-initiated, multi-centre, double-blinded, 2x2 factorial randomised trial comparing slower (333mL/hr) with faster (999 mL/hr) rates of intravenous fluid bolus infusions, as well as comparing Plasma-Lyte 148 with 0.9% saline for maintenance and bolus intravenous fluid. This chapter describes the comparison between the clinical effectiveness of a slower (333mL/hr) with faster (999 mL/hr) rates of intravenous fluid bolus infusions in critically ill patients.

The trial ran in 75 ICUs in Brazil between 2017 and 2020, with results presented at a Critical Care Reviews livestream on August 10th, 2021, with a simultaneous publication in *JAMA*. Eligible patients were being treated in the ICU, required volume expansion, were not expected to be discharged from ICU by the following day, and had 1 or more risk factor for adverse outcome (hypotension, sepsis, mechanical ventilation, oliguria, elevated serum creatinine or liver cirrhosis or failure). Patients were excluded if they required or were imminently expected to require renal replacement therapy, had severe electrolyte abnormalities, or whose death was imminently expected.

The slow rate group received all intravenous fluid boluses at a rate of 333 mL/hr for the duration of ICU stay, up to 90 days. The fast rate group received all intravenous fluid boluses at a rate of 999 mL/hr for the duration of ICU stay, up to 90 days.

The primary outcome was mortality at 90 days. Assuming 35% mortality for the 0.9% saline arm and a 5% significance level, the planned sample size of 11,000 would have 89% power to detect a 10% relative reduction in mortality. Interaction between the two interventions was analysed but not anticipated, and a recalculation of the sample size, based on the actual event rate, was planned for after recruitment of 1000 patients. Analyses were performed on an intention to treat basis, with 3 interim analyses over the course of the trial. Seven subgroups were pre-defined: sepsis, baseline acute kidney injury (AKI) (KDIGO stage 1), surgical patients, brain trauma, APACHE II score above/below 25, and patients in receipt of less than or greater than 1000 mL 0.9% saline in the 24 hours prior to randomisation.

The number of patients screened was not available, but 11,052 patients were randomised, of whom 532 were subsequently excluded due to lack of consent or duplicate randomisation. 10,520 patients were therefore analysed, 5276 in the slower infusion arm and 5244 in the faster infusion arm. A second randomisation assigned patients to either Plasma-Lyte 148 or 0.9% saline as the intravenous fluid to be used for bolus and maintenance infusions.

90-day mortality was almost identical between study arms: 26.6% for slower infusion rate versus 27.0% for faster infusion rate (hazard ratio after adjustment for site and several prognostic variables, 1.03; 95% CI, 0.96 to 1.11). There was no significant interaction between infusion rate and fluid type.

There were no significant differences between groups for any of the pre-specified subgroups. A large number of pre-specified sensitivity analyses was performed, such as a stratification analysis based on the presence or absence of heart failure at baseline. The only statistically significant finding was an exploratory analysis using Bayesian networks

which identified a slightly higher probability that patients were discharged alive from the ICU or no longer required vasopressors at day 3 in the slower infusion group. The magnitude of this effect was small (OR, 1.11; 95% CI, 1.01 to 1.21).

Volumes of fluid administered were similar between the two arms: with a mean of just over 1000 mL of bolus fluid on day 1, decreasing as expected on subsequent days. Over 98% of fluid challenges were administered per protocol.

Outcome	Slower infusion	Faster infusion	Measure of effect
AKI with requirement for RRT during hospital stay	397/5267 (7.5%)	423/5238 (8.1%)	OR, 0.92 (0.80 to 1.06)
AKI (KDIGO stage ≥2) up to day 7	288/1211 (23.8%)	265/1139 (23.3%)	OR, 1.00 (0.82 to 1.22)
Day 7 SOFA score, median (IQR)	4 (2-7)	4 (2-7)	-0.07 (-0.37 to 0.05)
Day 7 SOFA-cardiovascular score >2	403/1600 (25.5%)	426/1525 (27.9%)	OR 0.88 (0.75 to 1.04)
Day 7 SOFA-coagulation score >2	76/1600 (4.8%)	56/1525 (28.9%)	OR 1.37 (0.98 to 1.90)
ICU mortality	902/5267 (17.1%)	922/5238 (17.7%)	OR, 1.00 (0.89 to 1.12)
Hospital mortality	1190/5267 (22.6%)	1204/5238 (23.0%)	OR, 1.01 (0.91 to 1.12)
ICU length of stay, days (median, IQR)	3 (2 to 7)	3 (2 to 7)	Mean ratio 0.98 (0.93 to 1.03)
Hospital length of stay, days (median, IQR)	8 (5 to 19)	9 (5 to 17)	Mean ratio 0.99 (0.94 to 1.04)

Table 1: Key secondary and tertiary outcomes:

AKI, acute kidney injury; RRT, renal replacement therapy; KDIGO, Kidney Disease Improving Global Outcomes; SOFA, sequential organ failure assessment score; ICU, intensive care unit; IQR, interquartile range

Critique

BaSICS is one of the largest randomised trials ever conducted in critical care, and the only large trial comparing two alternative rates of intravenous bolus infusions in critically ill adults. As one of the most common interventions in critically ill, and indeed, hospitalised patients, intravenous fluid administration merits rigorous study and

understanding. Even a small effect on patient-centred outcomes from choice or method of fluid administration will impact on hundreds of thousands of patients each year, and so very large studies, adequately powered to detect small differences in patient-centred outcomes, are clearly warranted. BaSICS set out to answer the question of whether a slower (333 mL/hr) rate of fluid bolus infusion was beneficial when compared with a more usual approach of rapid infusion (999 mL/hr). The trial protocol and statistical analysis plan were pre-published and clearly describe the planned trial methodology.

Patients were a broad selection of 'all-comers' to critical care requiring at least one fluid bolus and all had at least one organ failure, although with median APACHE II scores of 12 and SOFA scores of 4, were at the less severe end of the critical illness spectrum, and nearly half were elective surgical patients. The setting was 75 ICUs across Brazil.
The trial was extremely well-conducted, with extremely high (well over 90%) protocol adherence despite the huge number of patients and sites. Unlike the fluid type randomisation, this was an open-label trial; blinding of clinical teams and investigators would have been nearly impossible.

There was limited data available on which to base the two interventions. Previous observational work on fluid bolus therapy has highlighted variability of practice with regard to fluid type, volume, rate, triggers, and endpoints, but as the trialists acknowledge, the choice of 333 mL/hr for the slower infusion group was essentially arbitrary. The only similar randomised trial, FEAST, was carried out in children with infection and shock in Sub-Saharan Africa, for whom access to intensive care was limited. The comparison was between rapid fluid boluses targeted at rapid restoration of perfusion versus a more gradual rehydration regimen. Applicability to an adult intensive care population is therefore uncertain. Moreover, the difference in treatment strategies in FEAST (fluid boluses compared with rehydration) was of a much greater magnitude than in BaSICS, so that a smaller effect size was always likely. Availability of other interventions (e.g. vasopressors and mechanical ventilation) in ICUs would provide further mitigation of any injury due to the speed of fluid bolus infusion.

The mean volume of fluid infused as boluses was around 1000 mL on day 1, decreasing on subsequent days. The total volume of fluid boluses infused was not reported. Of note, patients had received a median of 1000 mL intravenous bolus fluid in the 24 hours prior to study enrolment. Given knowledge of practice patterns, it is reasonable to assume this is most likely to have been administered at a rate closer to the faster rate of 999 mL/hr. While this represents a small proportion of the total fluid administered, if sufficient to activate mechanisms of injury, it may serve to reduce the effect of a slower infusion rate during ICU stay. It is necessary, therefore, to review the possible mechanisms by which rapid fluid infusion may be harmful.

Following publication of the FEAST trial,[1] in an exploratory analysis, cardiovascular collapse was identified as the primary mechanism of death associated with mortality in children receiving fluid bolus therapy.[3] Around the same time, a number of studies showed the potential of even small volumes (750 mL) of rapidly infused intravenous fluid to result in atrial natriuretic peptide (ANP) -mediated and direct hydrostatic pressure mediated injury to the endothelial glycocalyx, a thin layer of glycocosaminoglycans largely responsibly for maintaining barrier function and preventing fluid leak from capillaries.[4,5] As the endothelial glycocalyx is already injured in sepsis, a hypothesis emerged that rapid administration of intravenous fluid could exacerbate this, leading to a self-perpetuating capillary leak and haemodynamic instability, for which the treatment would often be more intravenous fluids and a requirement for higher vasopressor doses. Subsequently, in a sheep model of sepsis used to reproduce and explore this effect in greater detail, fluid resuscitation was shown to increase levels of ANP and of hyaluronan, a marker endothelial glycocalyx injury, followed by an increase in vasopressor dose.[6] Most, though not all, studies in human patients with sepsis have supported this hypothesis.[7–10] Assuming glycocalyceal injury to be at least one of the mechanisms by which rapid intravenous fluid therapy may be harmful, the effect seems to be of rapid onset after relatively low volumes of intravenous fluid.[1,3,7]

A very small effect was observed on cardiovascular stability in exploratory Bayesian analyses in this trial, consistent with the observed data from FEAST and other studies. However, this was likely of minimal clinical significance and not of the magnitude observed in other studies.[1,6,7] It does suggest the possibility of an effect, however, and it may be hypothesised that the difference in fluid infusion rates in this trial was simply not large enough to alter the course of disease. It may therefore be further hypothesised that in this trial in the ICU setting, the glycocalyceal injury was already well-established, with only a very small impact from the alternative fluid infusion rates studied here.

Where this sits in the body of evidence

BaSICS is the only large scale randomised controlled trial comparing two rates of fluid bolus administration in critically ill patients. Although informative to speculate on potential mechanisms of harm, the FEAST trial[1] studied a different question, in a different population, in a different setting. The FEAST trial compared three different resuscitation strategies in African children with shock and life threatening infection. 3141 children were randomised to receive a 0.9% saline bolus, a 5% human albumin solution bolus or no fluid bolus. The volume was 20 mL/kg administered over an hour. As such, a single rate of infusion was used and there was no comparison between a faster and slower rate of fluid bolus administration. Mortality at 48 hours was significantly

lower in the no fluid bolus group; albumin group (10.6%) vs saline group (10.5%) vs no bolus group (7.3%), a finding maintained at 28 days.

In the BaSICS trial, no differences in clinical outcomes were present between groups, and it is therefore likely that the rate at which fluid boluses are administered in ICU has little or no effect on patient-centred outcomes. However, the possibility of a very small effect cannot be ruled out, and given the ubiquity of the intervention, even that small effect could translate into meaningful benefit or harm at a population level. Future studies should address this question from the beginning of the patient journey in the emergency room through to the ICU, and should aim to separate the rates of fluid infusion to a greater degree.

Finally, however, the trial does show that the immediacy with which clinicians typically approach fluid bolus administration in the ICU may not be necessary, and that a slower correction of suspected hypovolaemia is safe. A slower infusion rate also allows for the intervention to be stopped when the desired endpoints are achieved, rather than reflex administration of a pre-specified intravenous fluid volume.

Should we use a slower or faster rate of infusion for intravenous fluid boluses in the ICU?

This should probably be on a case by case basis. Some patients require rapid fluid replacement, but for many, a slower infusion rate is adequate.

References

1. Maitland K, Kiguli S, Opoka RO, et al. Mortality after Fluid Bolus in African Children with Severe Infection. N Engl J Med 2011;364(26):2483-2495

2. Cecconi M, Hofer C, Teboul JL, et al. Fluid challenges in intensive care: the FENICE study: A global inception cohort study. Intensive Care Med 2015;41(9):1529-1537

3. Maitland K, George EC, Evans JA, et al. Exploring mechanisms of excess mortality with early fluid resuscitation: insights from the FEAST trial. BMC Med 2013;11:68

4. Powell MF, Mathru M, Brandon A, Patel R, Frölich MA. Assessment of endothelial glycocalyx disruption in term parturients receiving a fluid bolus before spinal

anesthesia: a prospective observational study. Int J Obstet Anesth 2014;23(4):330-334

5. Beiseigel M, Simon BT, Michalak C, Stickney MJ, Jeffery U. Effect of peri-operative crystalloid fluid rate on circulating hyaluronan in healthy dogs: A pilot study. Vet J Lond Engl 1997. 2021;267:105578

6. Byrne L, Obonyo NG, Diab SD, et al. Unintended Consequences: Fluid Resuscitation Worsens Shock in an Ovine Model of Endotoxemia. Am J Respir Crit Care Med 2018;198(8):1043-1054

7. Hippensteel JA, Uchimido R, Tyler PD, et al. Intravenous fluid resuscitation is associated with septic endothelial glycocalyx degradation. Crit Care Lond Engl 2019;23(1):259

8. Puskarich MA, Cornelius DC, Tharp J, Nandi U, Jones AE. Plasma syndecan-1 levels identify a cohort of patients with severe sepsis at high risk for intubation after large-volume intravenous fluid resuscitation. J Crit Care 2016;36:125-129.

9. Saoraya J, Wongsamita L, Srisawat N, Musikatavorn K. The effects of a limited infusion rate of fluid in the early resuscitation of sepsis on glycocalyx shedding measured by plasma syndecan-1: a randomized controlled trial. J Intensive Care 2021;9(1):1

10. Saoraya J, Wongsamita L, Srisawat N, Musikatavorn K. Plasma syndecan-1 is associated with fluid requirements and clinical outcomes in emergency department patients with sepsis. Am J Emerg Med 2021;42:83-89

BaSICS – Fluid Type

Effect of Intravenous Fluid Treatment With a Balanced Solution vs 0.9% Saline Solution on Mortality in Critically Ill PatientsThe BaSICS Randomized Clinical Trial. Zampieri FG, Machado FR, Biondi RS, Freitas FGR, Veiga VC, Figueiredo RC, et al. JAMA 2021;326(9):818-829

Introduction

Intravenous fluid administration is one of the most commonly-performed interventions in critically ill patients. An estimated 1 million litres of 0.9% saline is administered intravenously each day globally.[1] The worldwide market for this fluid was worth $2.88 billion US dollars in 2018 and is anticipated to rise to $3.71 billion by 2026.[1] However, despite this international growth of the saline market, its dominance is challenged by the narrative that 0.9% saline is nephrotoxic. In Australia, despite a year-on-year growth of 3-4% in hospital patients numbers, use of 0.9% saline have fallen slightly, from 7.4 to 7.3 million litres per year.[1] The difference has been taken up by balanced fluids, thought to be less nephrotoxic from their lower sodium load.[1]

The high sodium and chloride content of 0.9% 'normal' saline, 154 mmol/L, is associated with a number of adverse physiological consequences. Hyperchloraemia results in metabolic acidosis, renal afferent vasoconstriction, and reduced glomerular filtration.[2,3] Balanced salt solutions, such as Hartmann's or Ringer's solutions, or the more recently available Plasma-Lyte 148, have a lower sodium content, a non-chloride buffer (lactate or acetate) and more closely approximate the constituents of normal plasma. The choice of crystalloid is largely clinician-dependent, with widely different patterns of use in different regions.[4]

Previous observational and before-after studies provide evidence of increased rates of acute kidney injury and other adverse outcomes with greater exposure to 0.9% saline.[5,6] This was supported by the SMART cluster randomised trial[7] involving over 15,000 patients in 5 ICUs within a single hospital system in the USA. This study found better outcomes in the balanced crystalloid group, with a lower incidence of a composite primary endpoint of mortality, new renal replacement therapy or persistent renal dysfunction. Even a small effect on clinical outcomes attributable to choice of intravenous fluid would be of huge global importance.

Synopsis

The Balanced Solution Versus Saline in Intensive Care Study (BaSICS) sought to compare the clinical effectiveness of Plasma-Lyte 148, a balanced salt solution, with 0.9% saline with regard to 90-day mortality and other clinically-important endpoints in ICU patients.

BaSICS was an investigator-initiated, multi-centre, double-blinded, 2x2 factorial randomised trial comparing Plasma-Lyte 148 with 0.9% saline for maintenance and bolus intravenous fluid, as well as comparing two different rates of intravenous bolus fluid administration. The trial ran in 75 ICUs in Brazil between 2017 and 2020. The results were presented at a Critical Care Reviews livestream on August 10th, 2021 and published synchronously in JAMA.

Eligibility criteria included patients who required volume expansion, were not expected to be discharged from ICU by the following day, and had 1 or more risk factors for acute kidney injury (hypotension, sepsis, mechanical ventilation, oliguria, elevated serum creatinine or liver cirrhosis or failure). Patients were excluded if they required, or were imminently expected to require, renal replacement therapy, had severe electrolyte abnormalities, or whose death was imminently expected.

The Plasma-Lyte group received Plasma-Lyte 148 for all fluid boluses, maintenance fluids and drug infusions > 100mL for the duration of ICU stay, up to 90 days. The saline group received 0.9% saline used for all fluid boluses, maintenance fluids and drug infusions > 100mL for the duration of ICU stay up to 90 days.

The primary outcome was mortality at 90 days. Assuming a 35% mortality rate for the saline group, a sample size of 11,000 would have 89% power to detect a 10% relative reduction in mortality at the 5% significance level. Interaction between the two interventions was analysed but not anticipated, and a recalculation of the sample size, based on the baseline event rate was planned for after recruitment of 1000 patients. Analyses were performed on an intention-to-treat basis, with 3 interim analyses over the course of the trial. Seven subgroups were pre-defined: sepsis, baseline AKI (KDIGO stage 1), surgical patients, brain trauma, APACHE II score above/below 25, and patients in receipt of less than or greater than 1000 mL 0.9% saline in the 24 hours prior to randomisation.

The number of patients screened was not available, but 11,052 patients were randomised, of whom 532 were subsequently excluded due to lack of consent or duplicate randomisation. 10,520 patients were analysed, 5230 in the Plasma-Lyte 148 group and 5290 in the 0.9% saline group. A second randomisation assigned patients to either rapid or slow infusion rates of intravenous bolus fluid administration.

Groups were similar at baseline. Almost half of all patients were admitted to the ICU post elective surgery. Two-thirds received crystalloid fluid prior to being admitted to the ICU and almost half received greater than 1 L. On day one, patients in both groups

received a median of 1.5 L of their study fluid. The median (SD) total fluid administered after 3 days was 4.1 L (2.9), including 2.9 L (2.4) of study fluid.

90-day mortality was almost identical between study groups: 26.4% for Plasma-Lyte 148 versus 27.2% for 0.9% saline (HR after adjustment for site and several prognostic variables, 0.97; 95% CI, 0.90 to 1.05).

Outcome	*Plasma-Lyte 148*	0.9% Saline	Measure of effect
AKI with requirement for RRT during hospital stay	393/5218 (7.5%)	427/5287 (8.1%)	RR, 0.93 (0.81 to 1.06)
AKI (KDIGO stage ≥2) up to day 7	276/1180 (23.4%)	273/1170 (23.3%)	OR, 1.07 (0.88 to 1.30)
ICU mortality	907/5218 (17.4%)	922/5287 (17.4%)	OR, 1.01 (0.90 to 1.13)
Hospital mortality	1177/5218 (22.6%)	1217/5287 (23.0%)	OR, 0.98 (0.88 to 1.09)
ICU length of stay, days (median, IQR)	3 (2 to 7)	3 (2 to 7)	Mean ratio 0.99 (0.94 to 1.04)
Hospital length of stay, days (median, IQR)	8 (5 to 18)	9 (5 to 18)	Mean ratio 0.98 (0.93 to 1.03)

Table 2: Key secondary and tertiary outcomes

In patients with traumatic brain injury, mortality was higher in the Plasma-Lyte 148 group (31.3%) than the 0.9% saline group (21.1%) with a point estimate for the hazard ratio of 1.48 (95% CI, 1.03 to 2.12). In the remaining pre-specified subgroups, there was no difference in the primary outcome between treatment groups. A number of post-hoc sensitivity analyses were undertaken. When patients with traumatic brain injury were excluded, the results for primary and secondary endpoints remained similar between treatment groups. Other sensitivity analyses using varying definitions of AKI did not yield significantly different results to the main analysis. In a Bayesian network analysis, the use of Plasma-Lyte 148 was associated with a high probability of a Glasgow Coma Scale score ≤ 12 in patents still receiving mechanical ventilation at day 7. Of note, serum chloride levels were significantly higher from days 1 - 7 in patients in the 0.9% saline group than the Plasma-Lyte 148 group.

Critique

BaSICS is the largest randomised trial comparing balanced crystalloids with 0.9% saline ever to be conducted, and the achievement that its completion represents cannot be overstated. Over 11,000 patients were enrolled in less than 3 years in 75 ICUs, latterly during the COVID-19 pandemic. This demonstrates the huge capabilities inherent in a collaborative and well-functioning clinical trials group focused on answering important clinical questions, in this case BRICnet, the Brazilian Research in Intensive Care Network.

As one of the most common interventions in critically ill, and indeed, hospitalised patients, intravenous fluid administration merits rigorous study and understanding. Even a small effect on patient-centred outcomes from choice or method of fluid administration will impact on hundreds of thousands of patients each year, and so very large studies, adequately powered to detect small differences in mortality, are warranted. BaSICS set out to answer the question of whether a balanced crystalloid, Plasma-Lyte 148, offered improved clinical effectiveness for both bolus and maintenance fluid administration over 0.9% saline, considered to be the standard of care in Brazilian ICUs and in many institutions globally. The trial protocol and statistical analysis plan were pre-published and clearly describe the planned trial methodology.

Patients were a broad selection of 'all-comers' to critical care requiring at least one fluid bolus and all had at least one organ failure, although with median APACHE II scores of 12 and SOFA scores of 4, were at the less severe end of the critical illness spectrum, and nearly half were elective surgical patients. Given the appropriate focus on renal outcomes, patients with AKI were heavily represented, with nearly 80% KDIGO stage 1 or above. The setting was 75 ICUs across Brazil.

The trial was rigorously conducted, with reasonable protocol adherence (in the order of 80%), sufficient to produce a slight difference in serum chloride levels over the first 7 days, which was the main hypothesised mediator of effect. Although statistically significant separation was present, the clinical significance of an approximately 2 mmol/L difference in serum chloride could be questioned. In addition, as the trialists noted, a considerable proportion of the total intravenous fluid received was outside the study in the emergency department, operating room, or wards prior to ICU admission.

The estimated mortality of 35% on which the sample size was calculated proved to be high for a relatively low acuity cohort with many elective post-operative patients. Furthermore, the 10% relative hazard reduction on which the study was powered seems unrealistically large. For both of these reasons, it is likely that despite the very large sample size, it was simply underpowered to detect what is likely to be a much more modest effect. For example, a post-hoc power calculation based on a baseline mortality

of 27% (as in this trial) would imply the need for over 100,000 patients to be enrolled to achieve 85% power to detect a 3% reduction in the hazard of 90-day mortality. Clearly, while this is unlikely to be achievable at present, the ANZICS MEGA-ROX trial, aiming to recruit 40,000 patients exemplifies just how opinion and ambitions as to what is feasible are changing.

Where this sits in the body of evidence

A number of randomised trials have now addressed the question of whether balanced crystalloids or 0.9% saline are superior, with particular focus on acute kidney injury as an outcome.

In two very large cluster-randomised trials carried out in a single large medical centre in the USA, SMART[7] and SALT-ED,[8] Plasma-Lyte 148 and 0.9% saline were compared in cohorts of patients in intensive care units and in emergency departments respectively. In both trials, a small difference in major adverse kidney events (death, new RRT or persistent renal dysfunction – defined as an elevation in creatinine to ≥ 200% baseline) favoured the use of balanced crystalloids.

Subsequent to the publication of this trial, in the PLUS trial,[9] 5037 patients in ICUs in Australia and New Zealand were individually randomised to Plasma-Lyte 148 (balanced solution) or to 0.9% saline. Despite much greater exposure to study fluid (approximately 3800 mL) and higher chloride and lower pH levels in the 0.9% saline group, no differences in clinical outcomes were present between groups.

Hammond and colleagues carried out an up to date systematic review and Bayesian meta-analysis, totalling 13 randomised trials, including BaSICS and PLUS, comparing balanced crystalloids with 0.9% saline.[10] The main finding was a high probability that the average effect of using balanced crystalloids is to reduce mortality. Point estimates for the outcome of acute kidney injury and of receipt of RRT favoured balanced crystalloids, but this did not reach statistical significance using a frequentist model. The exception, however, was in patients with traumatic brain injury, in whom balanced crystalloids resulted in higher mortality.

The ongoing FISSH (fluids in septic shock) trial (clinicaltrials.gov NCY03677102) will focus on the most severely ill patients in whom it may be hypothesised that any outcome difference may be most pronounced.

Should we use balanced crystalloids or 0.9% saline for critically ill patients?

A balanced solution is probably the better choice for most patients, the main exception being traumatic brain injury, where 0.9% saline is the fluid of choice. For the individual patient, though, it probably doesn't make much difference.

References

1. Normal Saline for Parenteral Use Market Size, Growth | Report [2026] [Internet]. [cited 2022 Jun 4];Available from: https://www.fortunebusinessinsights.com/normal-saline-for-parenteral-use-market-104520

2. Choi JS, Yun D, Kim DK, et al. Hyperchloremia is associated with poor renal outcome after coronary artery bypass grafting. BMC Nephrol 2021;22(1):343

3. Handy JM, Soni N. Physiological effects of hyperchloraemia and acidosis. Br J Anaesth 2008;101(2):141–50

4. Hammond NE, Taylor C, Finfer S, et al. Patterns of intravenous fluid resuscitation use in adult intensive care patients between 2007 and 2014: An international cross-sectional study. PLOS ONE 2017;12(5):e0176292

5. Yunos NM, Bellomo R, Hegarty C, Story D, Ho L, Bailey M. Association Between a Chloride-Liberal vs Chloride-Restrictive Intravenous Fluid Administration Strategy and Kidney Injury in Critically Ill Adults. JAMA 2012;308(15):1566–72

6. Raghunathan K, Shaw A, Nathanson B, et al. Association between the choice of IV crystalloid and in-hospital mortality among critically ill adults with sepsis. Crit Care Med 2014;42(7):1585–91

7. Semler MW, Self WH, Wanderer JP, et al. Balanced Crystalloids versus Saline in Critically Ill Adults. N. Engl. J. Med. 2018;378(9):829–39

8. Self WH, Semler MW, Wanderer JP, et al. Balanced crystalloids versus saline in noncritically ill adults. N Engl J Med 2018;378(9):819–28

9. Finfer S, Micallef S, Hammond N, et al. Balanced Multielectrolyte Solution versus Saline in Critically Ill Adults. N. Engl. J. Med. 2022;386(9):815–26

10. Hammond NE, Zampieri FG, Di TGL, et al. Balanced Crystalloids versus Saline in Critically Ill Adults — A Systematic Review with Meta-Analysis. NEJM Evid 2022;1(2):EVIDoa2100010.

REALITY

Gregory Ducrocq G, Gonzalez-Juanatey JR, Puymirat E, Lemesle G, Cachanado M, Durand-Zaleski I, et al. Effect of a Restrictive vs Liberal Blood Transfusion Strategy on Major Cardiovascular Events Among Patients With Acute Myocardial Infarction and Anemia. The REALITY Randomized Clinical Trial. JAMA 2021;325(6):552-560

Introduction

Since the publication of the TRICC trial[1] in 1999, reporting no clear benefit from a liberal red cell transfusion threshold in ICU patients with anaemia, there has been much debate over whether this finding could be generalised to critically ill patients, either with or at risk of ischaemia, or more particularly, cardiac ischaemia.

While there are obvious theoretical reasons for treating anaemia in patients with ischaemia, such as increasing oxygen carrying capacity, there are equally theoretical reasons for not transfusing red cells. Transfused red cells can lose deformability, necessary to transit through capillaries; have reduced levels of 2,3-DPG, necessary for oxygen unloading in the tissues; absorb nitric oxide, increasing small vessel vasoconstriction; and increase blood viscosity. Although the critical haemoglobin concentration, the level at which oxygen consumption becomes supply dependent, is multifactorial and patient and pathology specific, in animals this in the region of 40 g/dL[2] and in healthy volunteer studies approximately 50 g/dL.[3] Case reports have noted patients surviving acute haemorrhage to haemoglobin concentrations as low as 0.7 g/dL without autologous transfusion.[4]

Trials of transfusion thresholds have been undertaken in the settings of general ICU,[1] post cardiac surgery,[5–7] post hip surgery,[8] septic shock,[9] and upper GI bleeding.[10] While a clear and obvious benefit from a liberal transfusion threshold is not apparent, it remains a current standard to consider a transfusion threshold of 8 g/dL in critically ill patients with acute coronary ischaemia.[11]

Synopsis

The REALITY trial aimed to determine if a restrictive red cell transfusion strategy (transfusion threshold haemoglobin ≤8 g/dL) was non-inferior to a liberal strategy (transfusion threshold haemoglobin ≤10 g/dL) in patients with acute myocardial infarction and anaemia. This was an open-label, randomised, parallel group, stratified, non-inferiority trial. It ran between 2016 and 2019 in 35 centres across France and Spain.

Eligible patients were adults hospitalised for an acute myocardial infarction and with a haemoglobin value of between 7 and 10 g/dL. Exclusion criteria included shock, defined as a blood pressure less than 90 mmHg with a low cardiac output state or the need for vasoactive support, post procedure myocardial infarction, occurring after either percutaneous coronary intervention or coronary artery bypass graft, large haemorrhage, blood transfusion in the past 30 days, or haematological malignancy.

Patients were randomised in a 1:1 ratio, with blocks of varying sizes from 2 to 6, stratified by centre, using a web based system.

Patients in the restrictive transfusion group could receive a red cell transfusion at a haemoglobin level of ≤8 g/dL, with a post transfusion target range of 8 to 10 g/dL. Patients in the liberal transfusion group had a threshold for transfusion of ≤10 g/dL and so all received a transfusion, with a post transfusion target range of ≥11 g/dL. These transfusion thresholds and targets were maintained for the duration of the hospital admission or until 30 days. Follow-up assessment was not blinded.

The primary outcome was a composite of major adverse cardiovascular events (MACE) at 30 days, defined as death, stroke, myocardial infarction, or emergency revascularisation. Based on anticipated event rates of 11% in the restrictive group and 15% in the liberal group, 300 patients per group were required to identify a non-inferiority margin corresponding to a relative risk of 1.25, with 80% power and with a 1-sided 97.5% confidence interval.

668 consecutive patients were enrolled and 342 randomised to the restrictive group and 324 to the liberal group. Groups had similar characteristics at baseline. The median age was 77 years, 58% were male, mean body mass index 26, 79% were hypertensive and 50% diabetic. Approximately 70% suffered an ST elevation myocardial infarction. 6.5% of patients were actively bleeding. 13% of the restrictive group, and 17.5% of the liberal group, had an active bleed, mostly either at the site of vascular access or the gastrointenstinal tract. Similar numbers of patients in each group underwent coronary angiography (~80%), percutaneous coronary intervention (~59%) and coronary artery bypass grafting (~4%)

The two groups underwent randomisation after a median delay post admission of 1.6 and 1.9 days. The haemoglobin levels immediately prior to randomisation were 9.0 and 9.1 g/dL, respectively. 35.7% of the restrictive group and 99.7% of the liberal group received at least 1 unit of red cells. More units of red cells were administered in the liberal group than in the restrictive group (758 vs 342). For those who received a red cell transfusion, a similar mean number of units were transfused per patient (2.0 each).

Leukodepleted blood of a similar storage age was used (median storage 20 vs 21 days, in the restrictive and liberal groups, respectively). Small numbers of other blood products were transfused. The lowest mean haemoglobin value per group was 8.3 and 8.8 g/dL, respectively. At discharge from hospital, the mean haemoglobin values were 9.7 (1.0) g/dL and 11.1 (1.4) g/dL in the restrictive and liberal group, respectively.

In the randomised population, 11.1% of the restrictive group, in comparison with 14.2% of the liberal group, suffered a major adverse cardiovascular event; difference – 3.1 (95% CI, -8.4 to 2.3); relative risk 0.78 (95% CI, 0.00 to 1.17). This result met the set threshold to be deemed noninferior. The results of the a priori per-protocol (n=666) analysis, and post hoc sensitivity analysis allowing for site effects, were similar and also met the noninferior threshold. In a preplanned analysis, the restrictive approach failed to meet the threshold for superiority.

Due to the risk of false positives from multiple comparisons, secondary outcomes were presented descriptively. All cause mortality was numerically higher in the liberal group, 5.6% vs 7.7%, which was driven by cardiovascular deaths (13 events vs 21 events). There were more episodes of recurrent myocardial infarction (2.1% vs 3.1%) in the liberal group. In addition, there were more episodes of recurrent ST elevation myocardial infarction (0 vs 3), type two myocardial infarction (2 vs 5) and emergency revascularisation (5 vs 6) in the liberal transfusion group . The results from the primary analysis were consistent across 12 subgroups: age, gender, weight, smoking status, Killip class, kidney function, ST- vs non ST-segment elevation myocardial infarction, presence or absence of diabetes, hypertension, dyslipidaemia, active bleeding, and hemoglobin levels at the time of randomization.

Overall, adverse event rates were again similar between the two groups at 11.7% and 11.1%, respectively. There were numerically more episodes of acute kidney injury in the restrictive group (9.7% vs 7.1%; 33 vs 23 episode), but more episodes of acute respiratory distress syndrome (1 vs 7), multi-organ dysfunction (1 vs 3) and infection (0 vs 5) in the liberal group.

Critique

REALITY is a long awaited trial investigating the efficacy of red cell transfusion in patients with ischaemia and/or infarction, in this instance myocardial infarction. The question as to which haemoglobin level to transfuse at has dogged clinicians for years. The landmark TRICC trial, published in 1999, comparing liberal and restrictive transfusions thresholds in critically ill patients, reported non-significantly better outcomes with the restrictive approach, but was clear to exclude patients with acute ischaemia from its conclusions. While multiple studies in the ICU have largely supported

these initial results, and corroborated findings of safety and decreased resource use, these trials also largely exclude actively or recently ischaemic patients.

The first point to consider is the premise of the trial. REALITY tests the overall balance of effects of both benefit and harm from transfusion in a population with acute myocardial infarction. The entire practice of transfusion in myocardial ischaemia is based on the concept of increasing oxygen delivery to acutely ischaemic tissues. This approach hinges on two issues; firstly, that the small decrease in haemoglobin, from 10 g/dL to 8 g/dL is harmful; and secondly, that restoring this haemoglobin level is beneficial.

Clearly, an exsanguinating patient benefits from both the maintenance of an effective circulating blood volume and oxygen carrying capacity, but whether a mild decrease in haemoglobin levels significantly impacts tissue oxygen tension and function is less clear, as is whether the transfusion of allogenic red blood cells both restores this mild defect and is beneficial. It has long been recognised that patients with cardiovascular disease and anaemia have worse outcomes than those without anaemia,[12] but whether this is both causal and modifiable is less clear. Anaemia is common in the critically ill, with two-thirds having a haemoglobin concentration less than 12 g/dL and almost a third a value of less than 10 g/dL.[13] Critically ill patients also tend to decrease their haemoglobin concentrations during their critical illness towards 10 g/dL, a feature which has been speculated to be an evolutionary adaptation for the prevention of infection, as the host sequesters iron, which bacteria need for multiplication.[14] Transfusion in the ICU is also associated with worse outcomes, again, likely a reflection of the severity of illness, with sicker patients needing more interventions, although the possibility of direct harm remains.[13,15,16]

The second point to consider is the timing of transfusion. The ischaemic event had to have occurred within 48 hours of hospital admission and enrolment into the trial could occur at any time during their admission. The restrictive group were randomised at a median (IQR) of 1.6 (0.8 to 3.6) days into their admission and the liberal group 1.9 (0.8 to 3.6) days into their admission. By then, they had undergone coronary revascularisation (59% percutaneous coronary intervention and 4% coronary artery bypass grafting), plus medical management in the form of antiplatelet, anticoagulation therapy and anti-ischaemic therapy. Arguably, for benefit to occur with red cell transfusion, there should be an ongoing area of ischaemic penumbra which could benefit from red cell transfusion and the theoretical increase in oxygen delivery with this approach. Perhaps a personalised approach, based on some measure of ischaemic penumbra such as cardiac magnetic resonance imaging, might be a superior approach. Such a potential evolution of strategy in the management of acute myocardial infarction in patients with anaemia would be built upon the knowledge gained by the REALITY trial.

The exclusion of patients with shock is both intriguing and appropriate. It is intriguing, as it further exemplifies the thinking which has pervaded since the TRICC trial 23 years ago – that red cell transfusion can improve a state of shock and that an anaemic patient in shock should presumably receive a red cell transfusion. Of course, a more appropriate response would be to determine the aetiology of the shock and treat the cause, but this may be overly nuanced to include in a trial protocol. It is appropriate, as it allows REALITY to add to the evidence base that in non-shocked anaemic patients with acute myocardial infarction, red cell transfusion does not improve outcomes, and may be harmful. By formulating the inclusion and exclusion criteria in this manner, the trialists allow the sequential testing of the next question in a subsequent trial which clearly follows from REALITY – would red cell transfusion be beneficial in patients with acute cardiogenic shock with anaemia?

The comparison with red cell transfusion in patients with acute brain injury with anaemia is illuminating. Overall, there appears to be no benefit from this practice, and similar to transfusion in acute myocardial infarction, it may be harmful.[17] Subgroup analysis of 67 patients with traumatic brain injury in the TRICC trial showed similar 30 day mortality (17% vs 13%, P = 0.64), as did the subgroup of 66 patients in the paediatric TRIPICU trial,[18] comparing transfusion thresholds of 7 g/dL and 9.5 g/dL in stable, anaemic critically ill children.

Three small randomised controlled trials also directly examined the effect of different transfusion thresholds in traumatic brain injury[19] and subarachnoid haemorrhage[20,21]. The factorial trial by Robertson,[19] examining erythropoietin and red cell transfusion in traumatic brain injury, randomised 99 patients to a haemoglobin transfusion threshold of 7 g/dL and 101 patients assigned to 10 g/dL. Those managed with the more restrictive transfusion threshold, and lower haemoglobin, had a non-significantly better primary outcome of the Glasgow Outcome Scale score, dichotomized as favorable (good recovery and moderate disability) or unfavourable (severe disability, vegetative, or dead) at 6 months post injury (33% vs 42.5%; P=0.28). Patients managed with the lower transfusion threshold had an decreased rate of thromboembolic events (OR, 0.32; 95% CI, 0.12 to 0.79, P = 0.009). The trial by Naidech[20] in 44 patients with subarachnoid haemorrhage and high risk of vasospasm randomised patients to target haemoglobin concentrations of at least 10 g/dL or 11.5 g/dL. With relatively high haemoglobin targets, this trial does little to address the question of permissive moderate anaemia in this setting, but again reflects the underlying belief that anaemia is harmful. Although absolute outcomes were numerically better with the higher haemoglobin target, none reached statistical significance. A small feasibility trial[21] of 44 patients with moderate-to-severe traumatic brain injury reported improved hospital mortality with a transfusion threshold of 9 g/dL vs 7 g/dL (1 vs 7; P = 0.048) and non-significantly improved

neurological status at 6 months (P=0.06). Taken together these three trials are small and should not influence clinical practice. A meta analysis[22] of all three confirmed a state of uncertainty with regard to the overall effect of transfusion in this population.

Where this sits in the body of evidence

The contemporary field of red cell transfusion thresholds in critical care began in earnest with the publication of the TRICC trial by Paul Hebert in 1999.[1] This open label, parallel group, randomised controlled trial allocated patients to liberal or restrictive transfusion groups. The liberal group had a transfusion threshold of a haemoglobin value < 7 g/dL, and a target haemoglobin range of 7 to 9 g/dL post transfusion. The liberal group had a transfusion threshold of 10 g/dL and a target range of 10 to 12 g/dL. Out of 2039 screened patients, 838 patients were within 72 hours of ICU admission and with a haemoglobin < 9 g/dL. They were randomised to either group in a 1:1 fashion. The patients in the restrictive group received less red cells (mean 2.6±4.1 units vs 5.6±5.3 units) and had a lower mean daily haemoglobin concentration (8.5±0.7 vs 10.7±0.7). There was no significant difference in the primary outcome of 30 day mortality, 18.7% vs 23.3%; difference 4.7%; 95% CI, 0.84 to 10.2; P=0.11. In subgroup analysis, those with an APACHE II score < 20 (8.7% vs 16.1%; P=0.03) and aged less than 55 years (5.7% vs 13.0%; P=0.02) had improved 30 day mortality. In the subgroup with clinically significant cardiac disease, 30 day mortality was similar (20.5% vs 22.9%, respectively; P=0.69). Of note, this trial used non-leukodepleted, which contrasts with current standards.

Hajjar and colleagues published the parallel group randomised controlled Transfusion Requirements After Cardiac Surgery (TRACS) trial in 2010.[5] This single-centre Brazilian non-inferiority trial randomised patients post cardiac surgery to maintain their haematocrit either > 30% or >24%. 502 patients after cardiac surgery involving cardiopulmonary bypass were recruited. The mean haemoglobin of the liberal group was maintained at 10.5 g/dL, in comparison with the restrictive group, with a mean of 9.1 g/dL. 78% of the liberal group and 47% of restrictive group received a red cell transfusion. There was no significant difference in the composite primary outcome of 30-day all-cause mortality and in-hospital severe morbidity (cardiogenic shock, acute respiratory distress syndrome, or acute renal injury requiring dialysis or hemofiltration); 10% liberal group vs 11% restrictive group; difference 1%; 95% CI, −6% to 4%; P=0.85). This met the predefined noninferiority margin of 8%.

The UK multi-centre TITRe2 randomised controlled trial also compared restrictive with liberal transfusion thresholds in a post cardiac surgery population.[6] The two transfusions thresholds were a haemoglobin < 7.5 g/dL or < 9 g/dL. 2007 patients were randomised and 2003 were analysed. More patients in the liberal group received a transfusion (92.2% vs 53.4%). The primary outcome was a composite of either an infection or an

ischaemic event within 3 months of randomisation. There was no statistically significant difference in the primary outcome between the two groups; restrictive group, 35.1% vs liberal group, 33.0%; OR, 1.11; 95% CI, 0.91 to 1.34; P=0.30. More patients died in the restrictive group (4.2% vs. 2.6%; HR, 1.64; 95% CI, 1.00 to 2.67; P=0.045).

The international, noninferiority Transfusion Requirements in Cardiac Surgery (TRICS) III trial compared restrictive and liberal transfusion strategies in adults undergoing cardiac surgery with cardiopulmonary bypass and with a moderate-to-high predicted risk of death.[7] The primary outcome was a composite of death from any cause, nonfatal myocardial infarction, stroke, or new-onset renal failure requiring renal replacement therapy. The noninferiority margin was set at 3%. The transfusion thresholds were < 7.5 g/dL and < 9.5 g/dL in the two groups. 5035 patients from 73 centres in 19 countries were randomised between 2014 and 2017. Patients had a preoperative baseline haemoglobin concentration of 13.1±1.8 g g/d/L. 53.2% of the restrictive group and 72.6% of the liberal group received at least 1 unit of red cells. The mean haemoglobin difference between the two groups was approximately 1 g/dL during the trial period. The rates of occurrence of the primary outcome were 11.4% in the restrictive-threshold group, and 12.5% in the liberal-threshold group (difference, −1.11% 95% CI, −2.93 to 0.72; OR, 0.90; 95% CI, 0.76 to 1.07; P<0.001 for noninferiority). Mortality was similar in the two groups, 3.0% in the restrictive-threshold group and 3.6% in the liberal-threshold group (odds ratio, 0.85; 95% CI, 0.62 to 1.16).

Published in 2014, the international TRISS trial compared transfusions thresholds of < 7 g/dL with < 9 g/dL in 998 patients with a haemoglobin level < 9 g/dL and with septic shock.[9] Both groups had a mean baseline haemoglobin concentration of 8.4 g/dL. The liberal group received approximately twice the number of red cell transfusions (3088 vs 1545). Less patients in the restrictive group received a transfusion (63.5% vs 98.8%). There was no statistically significant difference in 90-day mortality rates, restrictive group, 43.0% vs liberal group, 45.0%; RR 0.94; 95% CI, 0.78 to 1.09; P=0.44. Secondary outcomes were also similar between groups.

In an open label, parallel group, randomised trial, Villanueva and colleagues compared two red cell transfusion thresholds in 921 patients with severe acute upper gastrointestinal bleeding.[10] The thresholds were < 7 g/dL and < 9 g/dL. A transfusion was administered to 49% of the restrictive group and 86% of the liberal group. The restrictive transfusion strategy resulted in a higher survival at 6 weeks (95% vs. 91%; HR, 0.55; 95% CI, 0.33 to 0.92; P=0.02). There was a lower incidence of re-bleeding in the restrictive group (10% vs 16%;) and a reduced rate of adverse events (40% vs 48%; P=0.02). The mechanism of the beneficial effect from a restrictive transfusion strategy may have been a lower portal-pressure gradient in this group.

In 2011, Carson and colleagues published the results of the FOCUS trial, comparing liberal and restrictive transfusion strategy in adults aged over 50 with an acute hip fracture and with either a history of, or risk factors for, cardiovascular disease.[8] The transfusion thresholds were a haemoglobin concentration of < 10 g/dL or < 8 g/dL. 2016 patients were randomised in a 1:1 fashion to either group. Groups were similar at baseline. 75% of patients were female. The mean age was 82 years old. 42% had a femoral neck fracture and 51% an intertrochanteric fracture. 10% were resident in a nursing home. 55% underwent general anaesthetic and 45% spinal anaesthetic. Preoperative haemoglobin levels were similar at 11.3 g/dL each. The pre-transfusion mean haemoglobins were 9.2 and 7.9 g/dL in the liberal and restrictive groups, respectively. 41% of the restrictive group and 96.7% of the liberal group received at least 1 unit of red cells. There was no significant difference in the primary outcome of death or an inability to walk across a room without human assistance at day 60 (35.2% vs 34.7%; liberal vs restrictive; OR 1.01; 95% CI, 0.84 to 1.22). Other outcomes were also similar, including in-hospital acute coronary syndrome or death (4.3% vs 5.2%; difference, –0.9%; 99% CI, –3.3 to 1.6) and mortality at day 60 (7.6% vs 6.6%; difference, 1.0%; 99% CI, –1.9 to 4.0).

The TRIPICU trial[18] compared haemoglobin transfusion thresholds of 7 g/dL with 9.5 g/dL in 637 stable, critically ill children. It ran between 2001 and 2005 in 19 PICUs in Belgium, Canada, the UK and the USA. The average patient age was 3 years, weight 14.5 kg and haemoglobin concentration 8.0 g/dL. Those in the conservative transfusion threshold group received 44% less transfusions and had a lower mean haemoglobin concentration during the trial period (8.7 ± 0.4 g/dL vs 10.8 ± 0.5 g/dL; P<0.001). The primary outcome, episodes of new or progressive multiple-organ dysfunction syndrome, occurred with similar frequency in both groups (12% in the restrictive-strategy group,vs 12% in the liberal-strategy group; difference, 0.4%; 95%, –4.6 to 5.4).

Should our haemoglobin transfusion threshold for stable patients with acute myocardial infarction be < 8g/dL?

Probably. The findings of the REALITY trial support this strategy but are not definitive.

References

1. Hébert PC, Wells G, Blajchman MA, et al. A Multicenter, Randomized, Controlled Clinical Trial of Transfusion Requirements in Critical Care. N Engl J Med 1999;340(6):409–17

2. Walsh TS, Saleh E-E-D. Anaemia during critical illness. Br J Anaesth 2006;97(3):278–91

3. Weiskopf RB, Viele MK, Feiner J, et al. Human cardiovascular and metabolic response to acute, severe isovolemic anemia. JAMA 1998;279(3):217–21

4. Dai J, Tu W, Yang Z, Lin R. Intraoperative management of extreme hemodilution in a patient with a severed axillary artery. Anesth Analg 2010;111(5):1204–6

5. Hajjar LA, Vincent J-L, Galas FRBG, et al. Transfusion Requirements After Cardiac Surgery. JAMA 2010;304(14):1559–67

6. Murphy GJ, Pike K, Rogers CA, et al. Liberal or restrictive transfusion after cardiac surgery. N Engl J Med 2015;372(11):997–1008

7. Mazer CD, Whitlock RP, Fergusson DA, et al. Restrictive or liberal red-cell transfusion for cardiac surgery. N Engl J Med 2017;377(22):2133–44

8. Carson JL, Terrin ML, Noveck H, et al. Liberal or Restrictive Transfusion in High-Risk Patients after Hip Surgery. N Engl J Med 2011;365:2453–62

9. Holst LB, Haase N, Wetterslev J, et al. Lower versus higher hemoglobin threshold for transfusion in septic shock. N Engl J Med 2014;371(15):1381–91

10. Villanueva C, Colomo A, Bosch A, et al. Transfusion strategies for acute upper gastrointestinal bleeding. N Engl J Med 2013;368(1):11–21

11. Vlaar AP, Oczkowski S, de Bruin S, et al. Transfusion strategies in non-bleeding critically ill adults: a clinical practice guideline from the European Society of Intensive Care Medicine. Intensive Care Med 2020;46(4):673–96

12. Chatterjee S, Wetterslev J, Sharma A, Lichstein E, Mukherjee D. Association of Blood Transfusion With Increased Mortality in Myocardial Infarction: A Meta-analysis and Diversity-Adjusted Study Sequential Analysis. JAMA Intern Med 2013;173(2):132–9

13. Vincent JL, Baron J-F, Reinhart K, et al. Anemia and Blood Transfusion in Critically Ill Patients. J Am Med Assoc 2002;288(12):1499–507

14. Astin R, Puthucheary Z. Anaemia secondary to critical illness: an unexplained phenomenon. Extreme Physiol Med 2014;3(1):4

15. Corwin HL, Surgenor SD, Gettinger A. Transfusion practice in the critically ill. Crit Care Med 2003;31(12):S668

16. Corwin HL, Gettinger A, Pearl RG, et al. The CRIT Study: Anemia and blood transfusion in the critically ill—Current clinical practice in the United States. Crit Care Med 2004;32(1):39–52

17. Lelubre C, Bouzat P, Crippa IA, Taccone FS. Anemia management after acute brain injury. Crit Care 2016;20(1):152

18. Lacroix J, Hébert PC, Hutchison JS, et al. Transfusion Strategies for Patients in Pediatric Intensive Care Units. N Engl J Med 2007;356(16):1609–19

19. Robertson CS, Hannay HJ, Yamal J-M, et al. Effect of Erythropoietin and Transfusion Threshold on Neurological Recovery After Traumatic Brain Injury: A Randomized Clinical Trial. JAMA 2014;312(1):36–47

20. Naidech AM, Shaibani A, Garg RK, et al. Prospective, Randomized Trial of Higher Goal Hemoglobin after Subarachnoid Hemorrhage. Neurocrit Care 2010;13(3):313–20

21. Gobatto ALN, Link MA, Solla DJ, et al. Transfusion requirements after head trauma: a randomized feasibility controlled trial. Crit Care 2019;23(1):89

22. Zhang W, Du K, Chen X. Benefits of red blood cell transfusion in patients with traumatic brain injury. Crit Care 2019;23(1):218

Resuscitation Trials

TTM2

Dankiewicz J, Cronberg T, Lilja G, Jakobsen JC, Levin H, Ullén S, et al. Hypothermia versus Normothermia after Out-of-Hospital Cardiac Arrest. N Engl J Med 2021;384:2283-94

Introduction

The contemporary era of induced hypothermia for adult comatose survivors of out-of-hospital cardiac arrest (OHCA) began in 2002, when two trials were published in the same edition of the *New England Journal of Medicine*.[1,2] They reported improved outcomes with the use of therapeutic hypothermia in comatose survivors of a ventricular fibrillation out-of-hospital cardiac arrest. Although worldwide practice changed following these trials, both were relatively small and at risk of bias. A much larger subsequent study, the TTM trial, published in 2013, compared the management of comatose survivors of OHCA at either 33°C or 36°C and found little difference in outcomes between the groups.[3] The RINSE trial, published in 2016, instituted therapeutic hypothermia pre-hospital with the use of a rapid infusion of cold saline during the cardiac arrest.[4] This resulted in a lower rate of return of spontaneous circulation and no improvement in survival at hospital discharge.

Two further trials were published in 2019. The PRINCESS trial compared a trans-nasal cooling device intra-arrest with standard care, followed by induced hypothermia in both groups at 32°C to 34°C when in hospital.[5] The intervention group reached a core temperature < 34°C at a median of 77 minutes quicker. There was no statistically significant difference in the primary outcome of a cerebral performance category (CPC) score of 1 to 2 at 90 days, 16.6% in the intervention cooling group vs 13.5% in the control group (difference, 3.1%; 95% CI, −2.3% to 8.5%). The HYPERION trial, published in 2019, compared temperature management at 33°C with 37°C in 584 patients after either an in-hospital or out-of-hospital cardiac arrest with a non-shockable rhythm.[6] There was a large increase in the rate of survival with a CPC score of 1 or 2 in those managed at 33°C (10.2% vs 5.7%; difference, 4.5%; 95% CI, 0.1 to 8.9; P=0.04). Given the uncertainty in the field, and a lack of consistent benefit from therapeutic hypothermia in this broad population, both in-hospital and out-of-hospital, from shockable and non-shockable rhythms, the original TTM trialists performed a follow up trial to bring clarity to this area.

Synopsis

The TTM2 trial was an investigator-initiated, international, multi-centre, stratified, parallel group, open-label, randomised controlled trial comparing hypothermia with normothermia in adult survivors of out-of-hospital cardiac arrest.[7] The trial ran in 62

centres in 14 countries between 2017 and 2020. It was reported at a *Critical Care Reviews* trial results livestream on June 16th, 2021, with a simultaneous publication in the *New England Journal of Medicine*.

Eligible patients were comatose adults admitted to hospital after an out-of hospital cardiac arrest of presumed cardiac or unknown cause, with any intra-arrest rhythm. Unconsciousness was defined as an inability to obey verbal commands or have a response to painful stimuli (score < 4 on the Full Outline of Responsiveness scale). A spontaneous cardiac output for at least 20 minutes after a successful resuscitation from cardiac arrest was required. Patients had to be enrolled within 180 minutes of return of spontaneous circulation (ROSC) and be considered for admission to the ICU without restrictions or limitation placed on their care. Exclusion criteria included an unwitnessed cardiac arrest with an initial asystolic rhythm, a temperature below 30°C on admission to hospital, receiving extracorporeal membrane oxygenation (ECMO), pregnancy, intracranial haemorrhage, and severe chronic obstructive pulmonary disease with a requirement for long-term home oxygen therapy.

All patients were to be sedated and receive invasive mechanical ventilation. Patients were randomised to either the hypothermia group, with a post cardiac arrest temperature to be maintained at 33°C or the normothermia group, with a target temperature < 37.5°C, with cooling instituted at a temperature of 37.8°C to reduce the temperature to < 37.5°C. Conservative cooling measures, such as antipyretics and tepid sponging, were used until a target temperature of 37.8°C was reached, at which point active device-implemented cooling was started. Active cooling was with a temperature management device, such as cooling blankets or endovascular cooling catheter. The exact device was not stipulated and local preference was used. Cooling to the required temperature was initiated immediately post randomisation. Once the target temperature was reached, a maintenance phase was entered and lasted until 28 hours post randomisation. At this 28 hour time-point, patents in the hypothermia group received gradual rewarming at 0.33 °C per hour until normothermia was reached, a period lasting up to 12 hours. Sedation could be stopped from hour 40. Normothermia (36.5 to 37.7°C) was to be maintained until 72 hours post randomisation, unless the patient was awake and extubated. Neurological prognostication was allowed at 96 hours post randomisation and was undertaken by a physician blinded to the patients group allocation.

The primary outcome was death at 6 months. 1862 patients were required to identify an absolute 7.5% reduction in mortality, from 50% in the control group to 42.5% in the intervention group, with 90% power at the 5% significance level. 1900 patients were to be recruited to allow for possible loss to follow-up. Six pre-defined subgroups were

analysed – age, gender, bystander CPR, initial rhythm, time to ROSC, circulatory status on admission and severity classification, based on the Pittsburgh cardiac arrest category.

4355 patients were screened, 2455 patients were excluded, 1900 patients were randomised, with 949 allocated to the hypothermia group and 951 allocated to the normothermia group. For the primary outcome, 930 and 931 patients were analysed in the two groups, respectively. The most common reasons for exclusion from entry to the trial were a time period > 180 minutes from ROSC (n=794), a non-cardiac cause of the cardiac arrest (n=441), not being in a comatose state (n=248) and having limitations in care (n=237).

Groups were similar at baseline. The approximate characteristics included a mean age of 63 years, 80% being male, 35% having hypertension, 19% having diabetes mellitus, 16% having a previous myocardial infarction, 52% suffering the cardiac arrest at home, 91% having a witnessed cardiac arrest, 80% receiving bystander CPR, 73% having a shockable rhythm, a median duration of cardiac arrest of 25 minutes (IQR, 16 to 40), median times from ROSC to randomisation of 135 minutes, 40% had an ST elevation myocardial infarction and 30% were in shock. Baseline mean (SD) temperatures were very similar in the hypothermia and normothermia groups, at 35.3 (±1.1) and 35.4 (±1.1), respectively.

Patients in the hypothermia group reached a temperature of 34°C in a median time of 3 hours. Active, device delivered cooling was used in 95% of the hypothermia group and 46% of the normothermia group, with similar proportions of both groups receiving surface (~ 70%) and intravascular (~ 30%) cooling. 6% of the hypothermia group were rewarmed early due to cardiovascular instability, as permitted by the protocol. Temperatures between the two groups separated well during the initial 28 hour maintanence phase, with approximate values of 33.1°C and 37.1°C, and converged to similar values just above 37°C after 40 hours.

There was no significant difference in the primary outcome of death at 6 months, being 50% in the hypothermia group and 48% in the normothermia group (RR, 1.04; 95% CI, 0.94 to 1.14; P=0.37). This was consistent across the 6 pre-defined subgroups. Less than 1% of randomised patients lacked data for the primary outcome. Similarly, there were no significant differences in secondary outcomes. At 6 months, a poor functional outcome, defined as a modified Rankin scale score of 4 to 6 (4 = moderate disability, 5 = severe disability and 6 = death) occurred in 55% in both groups (RR, 1.00; 95% CI, 0.92 to 1.09). Health-related quality of life, measured on the EQ-5D-5L visual-analogue scale, was again similar in both groups, with a mean between-group difference in patients who survived to 6 months of −0.8 points (95% CI, −3.6 to 2.0). Arrhythmias with

haemodynamic compromise happened more often in the hypothermia group (24% vs 17%).

Critique

TTM2 is another landmark trial in the field of therapeutic hypothermia post cardiac arrest. Methodologically, it is extremely robust, with efforts at avoiding bias being so comprehensive as to include writing the paper in duplicate whilst blinded to the results.

The internal validity of the trial is exceptionally high. Hypothermia was induced quickly, both groups seperated to their target temperature ranges and stayed there for the duration of the 28 hour maintanence period, before the patients in the hypothermia group were slowly rewarmed back to normothermia over the next 12 hours. Sedation and neuroprognostication was protocolised, and neuroprognostication was undertaken in a blinded fashion. While much of the care was not mandated, in a large randomised controlled trial, effects from any intervention with the ability to alter outcome, such as rates of bystander CPR, would be expected to largely balance between groups. Even if observed measured baseline characteristics do not balance exactly between groups, other unmeasured characteristics may equally skew in the opposite direction.

The external validity of the trial is interesting to consider. Of 11 major trials examining hypothermia in adult cardiac arrest, 7 have been undertaken in Europe,[1,3,5–8] 2 in Australia,[2,4] one each in Canada[9] and the USA.[10] Although all have been set in high income countries, the baseline characteristics and healthcare systems of these patients may change from one geographical region to the next. Rates of bystander CPR in TTM2 were very high at 80%, which contrasts with the North American trials in Canada (68%)[9] and the USA (58%).[10] This is a known contributor to outcome when compared across different locations.[11] Bystander CPR may decrease the likelihood of a hypoxic-ischaemic brain injury,[12] which is the pathology therapeutic hypothermia is used to target. As such, trials with lower rates of bystander CPR could be argued to have potentially more patients with such a brain injury and a greater opportunity to benefit from therapeutic hypothermia. No beneficial effect was observed in either North American trial.

Various questions can be raised as to whether the trial asked the correct question. Should the therapeutic effect have been delivered more quickly, for longer, at a lower temperature, or via a specific cooling device. The TTM2 trial does not attempt to answer these directly, although subgroup analyses may contribute to the interpretation of these effects in light of other evidence. The results of this trial answer the question posed by this trial. For the external questions, some of which have been used as a criticism of the trial, the answers largely lie in other studies.

Two trials have attempted to institute therapeutic hypothermia during resuscitative efforts intra-arrest, using either cold saline[4] or a nasal cooling device[5]. Neither improved mortality or neurological recovery. A very recent trial used intra-arrest nasal cooling in refractory out-of-hospital cardiac arrest, but as part of a package of care including intra-arrest transfer, automated chest compressions and immediate percutaneous coronary intervention.[13] 31.5% of those treated with this eCPR bundle survived at 6 months with good neurological outcomes compared with 22.0% with standard care. Whilst there are spectacular case reports of survival with intact neurological function after prolonged cardiac arrest in patients with severe hypothermia, the hypothermia usually precedes the cardiac arrest[14] or occurs concurrently in episodes of submersion in cold water.[15] Similarly, in deep hypothermic circulatory arrest, again the hypothermia precedes the period of circulatory standstill. Whether there is benefit from instituting hypothermia after the initiation of spontaneous cardiac arrest is less clear. In animal studies, cerebral metabolism falls approximately 6-8% per degree celcius.[16] In an anaesthetised dog experiment, at 13°C the cerebral metabolic rate for oxygen was just 8% of that at 37°C.[17]

	Time to Temperature *(minutes)*	**Target Temperature**	**Time to Temperature *(minutes)***	**Target Temperature**
CAPITAL CHILL	436	(31°C)	324	(34°C)
TTM2	315	(<34°C)		
HYPERION	317	(33°C)		
TTM	270	(33°C)		
Kim	284	(34°C)	215	(34°C)
HACA	480	(<34°C)		
Bernard	120	(33.5°C)		

Table 3. Approximate times to achieve target temperatures.
Values are based on stated median figures in the published papers and are the total time from either ROSC or activation of Emergency Medical Services.

- *The two groups in the Kim paper are for VF (left column) and non-VF (right column) groups.*
- *TTM timings via a personal communication from Dr Niklas Nielsen*

A related point, which TTM2 can address, is the practical speed at which hypothermia may be induced. As the centres involved had significant expertise, it is likely, pending the development of new technology, that the TTM2 trial achieved as quick an induction of hypothermia as is presently possible. None of the other large scale trials, inducing

hypothermia from the emergency department onwards in a patients journey, achieved quicker times to hypothermia.

One large scale international randomised controlled trial has compared a 24 hour period with a 48 hour period of therapeutic hypothermia at 33°C. In 355 adult comatose survivors of cardiac arrest, there were no siginificant differences in the primary outcome of good neurological outcome at 6 months (CPC 1 to 2) at 69% vs 64%, respectively; RR, 1.08; 95% CI, 0.93 to 1.25; P = 0.33.

Although slightly different temperature ranges have been studied in the majority of prior trials, most compare the range of 32°C to 34°C with 36°C to 38°C, or no intervention. The CAPITAL CHILL trial compared a temperature of 31°C with 34°C in 367 comatose survivors of out-of-hospital cardiac arrest. Hypothermia was maintained at these target temperatures for 24 hours. There was no difference in the composite primary outcome of mortality or poor neurologic outcome at 180 days; 48.4% vs 45.4%, in the 31°C group vs 34°C, group, respectively (RR, 1.07; 95% CI, 0.86 to 1.33; P = 0.56). Equally, the small blinded, randomised FROST-I trial compared 32°C (n = 52), 33°C (n = 49) and 34°C (n=49) in a similar out-of-hospital cardiac arrest population. Again, there was no difference in the primary outcome of survival with good neurologic outcome, defined as a modified Rankin Scale score of ≤ 3 at 90 days; 65.3%, 65.9% and 65.9%, respectively.

The issue as to the superiority of a specific cooing device was addressed in the ICEREA trial, which compared endovascular with surface cooling in 400 patients. Although use of the endovascular catheter resulted in faster and more tightly controlled hypothermia at the target temperature of 33°C, there was no significant difference in the primary outcome of survival with good neurological function (CPC 1 to 2) at day 28; 36% vs 28.4%, in the endovascular and surface cooling device groups, respectively (OR, 1.41; 95% CI, 0.93 to 2.16; P=0.107).

The evidence to date forces the question as to whether induced therapeutic hypothermia, as and when it is currently delivered, is simply ineffective and the results in the two original trials were chance findings due to intrinsic bias. The next trial in the TTM series of trials will investigate whether it is not hypothermia which is effective per se, but rather the avoidance of fever in this patient population.

Where this sits in the body of evidence

In 2002, Bernard and colleagues reported the results of a Australian multi-centre, randomised, open-label trial investigating therapeutic hypothermia in 275 comatose patients who had survived an out-of-hospital cardiac arrest. Patients in the hypothermia group were managed at a temperature of 32°C to 34°C, which was maintained for 24

hours, followed by passive rewarming to normothermia over 8 hours. The primary outcome was a favourable neurological outcome at 6 months, defined as a Pittsburgh Cerebral-Performance category score of 1 (good recover) or 2 (moderate disability). This occurred in 55% of the hypothermia group and 39% of the normothermia group (RR, 1.40; 95% CI, 1.08 to 1.81; P=0.009). Mortality at 6 months was also lower in the hypothermia group (41% vs 55%; RR, 0.74).

The HACA study randomised 275 patients after out-of-hospital cardiac arrest due to ventricular fibrillation or tachycardia, and unresponsive to voice after achieving ROSC, to therapeutic hypothermia or standard care. Therapeutic hypothermia (target 32 - 34°C) was maintained for 24 hours followed by 8 hours of passive rewarming. The primary endpoint of favourable neurological outcome was seen in 55% of the therapeutic hypothermia group and 39% in the normothermia group (RR, 1.40; 95% CI, 1.08 to 1.81). After adjustment for baseline imbalances, hypothermia was associated with reduced mortality (RR, 0.62; 95% CI, 0.36 to 0.95).

In a study of 1,359 patients with out-of-hospital cardiac arrest who achieved ROSC, participants were randomised to standard care or 2 L of intravenous saline at 4°C.[10] Intravenous cold saline decreased patient temperature by 1.2 to 1.3°C and reduced the mean time to reach 34°C (P < 0.001). There was no difference in the primary outcome measure of survival to hospital discharge; in those with VF, cold saline group, 62.7% (95% CI, 57.0% to 68.0%) vs control group, 64.3% (95% CI, 58.6% to 69.5%) (P = 0.69); in those without VF; cold saline group, 19.2% (95% CI, 15.6% to 23.4%) vs control group, 16.3% (95% CI, 12.9% to 20.4%) (P = 0.30). There was no difference in neurological outcome. There was a higher incidence of rearrest during transport in the cold saline group (26% vs. 21%; P = 0.008).

The TTM trial compared in-hospital cooling to 33°C with 36°C in 950 patients who had suffered an out-of-hospital cardiac arrest (irrespective of rhythm) and had a Glasgow Coma Scale score < 8.[3] The cooling intervention lasted for 24 hours and temperature was controlled to < 37.5°C for 72 hours. Cooling could be achieved by intravenous ice cold fluids, application of ice packs or commercially available cooling devices. There was no difference in 180 day mortality; 50% in the 33°C group compared to 48% in the 36°C group (HR, 1.06; 95% CI, 0.89 to 1.28; P = 0.51). There was no difference in the combined secondary endpoint of death or poor neurological outcome at 180 days (RR, 1.04; 95% CI, 0.89 to 1.17; P = 0.67).

The THAPCA-IH trial randomised 329 children aged 38 weeks to 18 years to therapeutic hypothermia (33.0 ± 1.0°C for 48 hours followed by maintenance of normothermia up to 120 hours) or normothermia following in-hospital cardiac arrest (IHCA).[18] Patients were

required to be within 6 hours of ROSC and dependant on mechanical ventilation. There was no significant difference in the primary outcome of favourable neurobehavioral score at 12 months between the two groups; 36% vs. 39% in the hypothermia and normothermia groups, respectively (RR, 0.92; 95% CI, 0.67 to 1.27; P = 0.63). The investigators intended to recruit 558 patients but the trial was terminated early following an interim analysis on the basis of futility.

The THAPCA-OH trial examined cooling after out-of-hospital cardiac arrest and recruited patients from 38 ICUs in the United States and Canada.[19] 295 children who remained comatose after out-of-hospital cardiac arrest were allocated to therapeutic hypothermia (33.0 ± 1.0°C) or therapeutic normothermia (36.75 ± 0.75°C). The treatment was commenced within 6 hours of ROSC. In contrast to the THAPCA-IH trial, the children in this trial were older (median age 2 years), 52% had no pre-existing medical conditions and 72% had a respiratory cause for their cardiac arrest. Asystole was the initial rhythm in 58% of cases. There was no difference in the primary outcome measure of survival at 12 months with a favourable neurobehavioral score; hypothermia group, 20% vs normothermia group, 12% (RR, 1.54; 95% CI, 0.86 to 2.76; P = 0.14). There was no difference in survival at 12 months; 38% vs. 29% in the hypothermia and normothermia groups respectively (P = 0.13).

The RINSE trial compared standard care with intra-arrest cooling achieved by administration of cold intravenous saline (3°C) in patients who had suffered an out-of-hospital cardiac arrest.[4] The trial was terminated early after recruitment of 1198 of a planned 2512 patients, due to changes in in-hospital temperature targets following the publication of the TTM trial. The temperature on arrival to hospital was lower in the intra-arrest cooling group; 34.7 ± 1.2°C vs 35.4 ± 1.3°C (P < 0.001). There was no difference in the primary outcome measure of survival to hospital discharge; 10.2% vs 11.4% in the intra-arrest cooling and standard care groups, respectively (P = 0.51). The intra-arrest cooling group had increased duration between arrival of emergency medical services and achieving ROSC (22.6 min vs 20.0 min, P=0.01), increased rates of death at scene (50.8% vs 45.3%, P = 0.06) and fewer patients transported with ROSC (33.5% vs 39.1% P = 0.04).

In 2019, Lascarrou and colleagues reported the results of the French multi-centre, open-label, HYPERION trial, comparing therapeutic hypothermia at 33°C ± 0.5°C with normothermia at 37°C in 584 patients comatose patients after suffering an in-hospital cardiac arrest with a non-shockable rhythm.[6] Patients in the hypothermia group had a temperature of 33°C ± 0.5°C maintained for 24 hours, followed by gradual rewarming at a rate of 0.25 to 0.50°C per hour, to 36.5 to 37.5°C, which was maintained for 24 hours. Those in the normothermia group had their temperatures maintained at 37°C ± 0.5°C for

48 hours. Patients in the hypothermia group had a higher rate of survival with a CPC scores of 1 (good cerebral performance or minor disability) or 2 (moderate disability), 10.2% vs 5.7% (difference, 4.5%; 95% CI, 0.1 to 8.9; P=0.04). 90-day mortality was similar in both groups, 81.3% and 83.2%, in the hypothermia and normothermia groups, respectively (difference, −1.9%; 95% CI, −8.0 to 4.3).

The Canadian single-centre, blinded, randomised controlled trial CAPITAL CHILL trial compared two different hypothermia targets, 31 °C and 34 °C, in 399 comatose survivors of out-of-hospital cardiac arrest.[9] Patients with both shockable and non-shockable rhythms were included. Cooling was started pre-hospital with ice-packs and continued with the use of endovascular cooling catheters. Hypothermia was maintained for 24 hours followed by a gradual rewarming at 0.25 °C/h until a temperature of 37 °C was reached. In the primary analysis, including 367 patients, there was no significant difference in the primary outcome of mortality or poor neurologic outcome at 180 days, 48.4%, vs 45.4%, in the 31 °C and 34 °C groups, respectively (RR, 1.07; 95% CI, 0.86 to 1.33; P = 0.56).

In February 2022, Bělohlávek and colleagues reported the results of the single-centre randomised controlled Prague Out-of-Hospital Cardiac Arrest study, investigating a package of interventions including mechanical chest compression, nasal cooling, intra-arrest transport, and immediate coronary angiography and intervention in patients suffering refractory out-of-hospital cardiac arrest.[13] The control group received standard care. Although the trial was stopped early for futility after recruitment of 264 patients, there was numerically a large difference in the primary outcome of survival at 6 months with good neurological recovery; eCPR group vs control, 31.5% vs 22.0% (difference 9.5%; 95% CI, −1.3 to 20.1%; P=0.09). The secondary outcomes were coherent with the primary outcome, with a significant increase in survival at 30 days with good neurological recovery (30.6% vs 18.2%; difference, 12.4%; 95% CI, 1.9 to 22.7; P=0.02) and cardiac recovery at 30 days (43.5% vs 34.1%; difference 9.4%; 95% CI, −2.5 to 21%; P=0.12).

Following the publication of the TTM2 trial in June 2021, The International Liaison Committee on Resuscitation Advanced Life Support Task Force produced an updated systematic review and meta analysis on temperature management in comatose adults following cardiac arrest.[20] Six trials were included in a meta analysis comparing a target temperature range of 32 to 34°C with normothermia, usually with the avoidance of pyrexias. The induction of hypothermia at a target of 32 to 34°C did not result in an improvement in survival at 90 to 180 days (RR, 1.08; 95% CI, 0.89 to 1.30) or a favorable neurologic outcome, again at 90 to 180 days (RR, 1.21; 95%CI, 0.91 to 1.61).

Should we routinely induce hypothermia in comatose survivors of out-of-hospital cardiac arrest?

No, there is now a wealth of evidence showing this is likely an ineffective therapy as currently used

References

1. Hypothermia after Cardiac Arrest Study Group. Mild therapeutic hypothermia to improve the neurologic outcome after cardiac arrest. N Engl J Med 2002;346(8):549–56.

2. Bernard SA, Gray TW, Buist MD, et al. Treatment of comatose survivors of out-of-hospital cardiac arrest with induced hypothermia. N Engl J Med 2002;346(8):557–63.

3. Nielsen N, Wetterslev J, Cronberg T, et al. Targeted temperature management at 33 C versus 36 C after cardiac arrest. N Engl J Med 2013;369(23):2197–206.

4. Bernard SA, Smith K, Finn J, et al. Induction of therapeutic hypothermia during out-of-hospital cardiac arrest using a rapid infusion of cold saline: the RINSE trial (rapid infusion of cold normal saline). Circulation 2016;134(11):797–805.

5. Nordberg P, Taccone FS, Truhlar A, et al. Effect of trans-nasal evaporative intra-arrest cooling on functional neurologic outcome in out-of-hospital cardiac arrest: the PRINCESS randomized clinical trial. JAMA 2019;321(17):1677–85.

6. Lascarrou J-B, Merdji H, Le Gouge A, et al. Targeted temperature management for cardiac arrest with nonshockable rhythm. N Engl J Med 2019;381(24):2327–37.

7. Dankiewicz J, Cronberg T, Lilja G, et al. Hypothermia versus normothermia after out-of-hospital cardiac arrest. N Engl J Med 2021;384(24):2283–94.

8. Deye N, Cariou A, Girardie P, et al. Endovascular versus external targeted temperature management for patients with out-of-hospital cardiac arrest: a randomized, controlled study. Circulation 2015;132(3):182–93.

9. Le May M, Osborne C, Russo J, et al. Effect of moderate vs mild therapeutic hypothermia on mortality and neurologic outcomes in comatose survivors of out-of-hospital cardiac arrest: the CAPITAL CHILL randomized clinical trial. JAMA 2021;326(15):1494–503.

10. Kim F, Nichol G, Maynard C, et al. Effect of prehospital induction of mild hypothermia on survival and neurological status among adults with cardiac arrest: a randomized clinical trial. JAMA 2014;311(1):45–52.

11. Girotra S, van Diepen S, Nallamothu BK, et al. Regional variation in out-of-hospital cardiac arrest survival in the United States. Circulation 2016;133(22):2159–68.

12. Kragholm K, Wissenberg M, Mortensen RN, et al. Bystander efforts and 1-year outcomes in out-of-hospital cardiac arrest. N Engl J Med 2017;376(18):1737–47.

13. Belohlavek J, Smalcova J, Rob D, et al. Effect of Intra-arrest Transport, Extracorporeal Cardiopulmonary Resuscitation, and Immediate Invasive Assessment and Treatment on Functional Neurologic Outcome in Refractory Out-of-Hospital Cardiac Arrest: A Randomized Clinical Trial. JAMA 2022;327(8):737–47.

14. Kuhnke M, Albrecht R, Schefold JC, Paal P. Successful resuscitation from prolonged hypothermic cardiac arrest without extracorporeal life support: a case report. J Med Case Reports 2019;13(1):1–4.

15. Bolte RG, Black PG, Bowers RS, Thorne JK, Corneli HM. The use of extracorporeal rewarming in a child submerged for 66 minutes. JAMA 1988;260(3):377–9.

16. Rosomoff HL, Holaday DA. Cerebral blood flow and cerebral oxygen consumption during hypothermia. Am J Physiol-Leg Content 1954;179(1):85–8.

17. Michenfelder JD, Milde JH. The effect of profound levels of hypothermia (below 14 C) on canine cerebral metabolism. J Cereb Blood Flow Metab 1992;12(5):877–80.

18. Moler FW, Silverstein FS, Holubkov R, et al. Therapeutic hypothermia after in-hospital cardiac arrest in children. N Engl J Med 2017;376(4):318–29.

19. Moler FW, Silverstein FS, Holubkov R, et al. Therapeutic hypothermia after out-of-hospital cardiac arrest in children. N Engl J Med 2015;372(20):1898–908.

20. Granfeldt A, Holmberg MJ, Nolan JP, et al. Targeted temperature management in adult cardiac arrest: Systematic review and meta-analysis. Resuscitation 2021;167:160–72.

Appendix – times to target temperature

- HACA median time to target temperature of 32°C to 34°C was 8 hours post ROSC
- HYPERION median time 317 minutes from randomisation to target hypothermia (IQR, 214 to 477); ROSC to randomisation were medians 232.5 and 219 mins
- Bernard 2 hours to 33.5°C post ROSC
- CAPITAL CHILL median time to target temperature was 208 minutes (IQR, 163-282) (31 °C group) and 120 (IQR, 80-174) (34°C group) from randomisation; time 911 call to randomisation was 228 minutes and 204 minutes in the two groups)
- TTM time from ROSC to temperature < 34°C
- TTM2 cardiac arrest to randomisation 135 minutes, time to target temperature 3 hours from start of intervention
- Kim emergency medical services call to randomisation 32 to 35 minutes; time to goal temperature, 4.2 hours and 3.0 hours in VF and non-VF groups (time points unclear)
- RINSE - unclear

VAM-IHCA

Andersen LW, Isbye D, Kjærgaard J, Kristensen CM, Darling S, Zwisler ST, et al. Effect of Vasopressin and Methylprednisolone vs Placebo on Return of Spontaneous Circulation in Patients With In-Hospital Cardiac Arrest. A Randomized Clinical Trial. JAMA 2021;326(16):1586-1594

Introduction

The primary aim of a resuscitation in cardiac arrest is the restoration of a spontaneous circulation. The longer the duration of the cardiac arrest, the greater the probability of both a failed resuscitation and a hypoxic-ischaemic brain injury should the circulation be belatedly restored. The duration of cardiac arrest required for the development of a brain injury is patient specific, with a clear threshold not obvious upon review of over 100,000 cases in a systematic review.[1]

Approximately 290,000 patients suffer an in-hospital cardiac arrest per year in the USA, with approximately one-quarter surviving to hospital discharge.[2] Over the past two decades, the trend for advanced life support guidance has been the gradual removal of drugs with pharmacologically sound rationale, but for which the available evidence does not support an improvement in outcomes with their use.

Bucking this trend has been the investigation of the combination of intra-arrest methylprednisolone and vasopressin, plus post arrest hydrocortisone for persisting circulatory shock. Corticosteroids have a wide array of effects, including a permissive effect on vasopressors, as well as being anti-inflammatory and anti-apoptotic, resulting in reduced organ injury.[3] Vasopressin acts on V1 receptors to increase vasoconstriction, and thus coronary perfusion pressure during cardiac arrest, which is a prime determinant of a successful return of spontaneous circulation (ROSC).[4] For survivors of cardiac arrest who remain in circulatory shock, the addition of intermittent administration of hydrocortisone may improve the resolution of hypotension and circulatory failure.[5]

Two small trials, one a single centre[6] and the other a three centre study,[5] by a single Greek group have been performed to date using this strategy. Both trials reported improved rates of ROSC and medium-term patient centred outcomes, including length of ICU and hospital stay, and 28 day mortality. To provide further clarity on the efficacy of this group of drugs, a Danish group completed a larger multi-centre trial.

Synopsis

The VAM-IHCA trial was an investigator-initiated, parallel-group, blinded, randomised controlled, superiority trial undertaken in 10 Danish hospitals between October 2018 and January 2021. Eligible patients were adults undergoing resuscitative attempts from an in-hospital cardiac arrest and who had received at least 1 dose of adrenaline. Trial specific exclusion criteria included the presence of mechanical circulatory support, cardiac arrest commencing out-of-hospital, a do-not-resuscitate from cardiac arrest order, prior enrolment in the trial and pregnancy.

Patients were allocated in a 1:1 fashion to the intervention or control group in random block sizes of 2, 4 or 6. Randomisation was stratified by site. The allocation list was produced by an independent statistician using a random number generator.

The intervention consisted of 40 mg methylprednisolone and 20 IU vasopressin administered intravenously as soon as possible after the first dose of adrenaline was given, as described by the European Resuscitation Council guideline 2015. A further three doses of 20 IU vasopressin could be administered after each subsequent dose of adrenaline, up to a total of 80 IU. The matching placebos for both vasopressin and methylprednisolone were 0.9% saline solutions, which were visually indistinguishable from the study drugs. The study drugs were brought to the cardiac arrest by a member of the trial team. They were prepared by a member of the cardiac arrest team, a process which was expected to take less than 1 minute.

The primary outcome was the rate of ROSC, defined as a spontaneous circulation with no further need for chest compressions for at least 20 minutes. Key secondary outcomes were survival at 30 days and survival at 30 days with a favourable neurological outcome, defined as a Cerebral Performance Category (CPC) score of 1 or 2. Based on Danish data, the control group was expected to have a 45% rate of ROSC. Consistent with the Greek VSE studies, the intervention group was anticipated to have a rate of ROSC of 58%. Using a x^2 test, 492 patients were required to identify this 13% difference with 80% power at the 5% significance level. Findings for secondary outcomes were considered exploratory due to the risk of multiple testing. Five subgroups were defined a priori – initial rhythm, whether witnessed or unwitnessed cardiac arrest, patient age, time from cardiac arrest to first administration of study drug, and time from adrenaline administration to study drug administration. Patients were followed-up for 90 days initially, although 6 month and 1 year outcomes will also be collected and later presented elsewhere. 30- and 90-day follow-ups were via telephone calls with the patient or surrogate, unless the patient was still in hospital, where it was conducted face-to-face.

2362 patients suffering in-hospital were screened and 512 randomised. The main reasons for exclusion were non-receipt of adrenaline, ROSC prior to trial drug administration, early termination of resuscitation, clinical team forgetting and clinician preference. 245 patients were randomised to the intervention group and 267 to the control group, with 237 and 264 analysed, respectively. Patients were excluded at this point largely for having pre-existing do-not-resuscitate orders or having an out-of-hospital cardiac arrest. Groups were similar at baseline, and received similar intra- and post- arrest care. The mean patient age was 71 years and 64% were male. 66% of patients were on a medical or surgical ward, 8% were in the ICU and 11% were in the Emergency Department. 54% had an initial rhythm of pulseless electrical activity and 35% asystole. 63% had a presumed cardiac or pulmonary cause of their cardiac arrest. The cardiac arrest team arrived a median of 3 minutes. The median times from recognition of cardiac arrest to first adrenaline administration was 5 minutes and to study drug administration 8 minutes. Compliance with administration of study drugs was high – 98.5% received the vasopressin/placebo trial drug and 97% received the methylprednisolone/placebo trial drug. The median number of administered doses of adrenaline was 3. For those receiving vasopressin/placebo, 28% received 1 dose, 29% received 2 doses, 16% received 3 doses and 26% received 4 doses.

More patients in the intervention group achieved ROSC: 42% vs 33%; RR, 1.30; 95% CI, 1.03 to 1.63; risk difference, 9.6%; 95% CI, 1.1% to 18.0%; P = 0.03. This occurred at median times of 16 and 18 minutes in the intervention and control groups, respectively. Survival at day 30 was numerically lower in the intervention group: 9.7% vs 12%, respectively; RR, 0.83; 95% CI, 0.50 to 1.37; risk difference, –2.0%; 95% CI, –7.5% to 3.5%; P = 0.48. There was no difference in the rates of survival at 30 days with a good neurological outcome (CPC score 1 or 2) , with 7.6% achieving this in both groups. Other outcomes, including post cardiac arrest organ dysfunction (SOFA score), number of days free of mechanical ventilation or vasopressors, discharge destination and health-related quality of life measures at 30 and 90 days. Episodes of harm were similar between the groups. All outcomes were consistent across the 5 pre-defined subgroups.

Critique

Building on the two initial studies in the field by Mentzelopolous, Andersen and colleagues sought to advance our understanding of the role of steroids and vasopressin in cardiac arrest by conducting a larger, multi-centre, randomised controlled trial. The question, interventions, control and outcomes used were all appropriate. The interventions were delivered in a blinded fashion and the vast majority of patients were treated as per the protocol, with resulting high internal validity. For any comparable well resourced healthcare system, the trial and results should be generalisable.

VAM-IHCA raises a number of interesting questions. Firstly, how does the combination of methylprednisolone and vasopressin lead to improved rates of ROSC, but lower survival at 30 days? How might vasopressin or methylprednisolone, or the combination, produce an immediate survival benefit but a later survival deficit. A comparison of the causes of death between the two groups is instructive. 76 patients died late in the vasopressin and methylprednisolone group, in comparison with 54 in the control group. Interestingly, there were less deaths related to circulatory dysfunction / failure in the intervention group: sudden cardiac arrest (n=2 vs n=4) and haemodynamic (otherwise unspecified) (n=11 vs n=31). This finding of a more robust circulatory system might be considered to be reflective of the additional support afforded by the combination of vasopressin and hydrocortisone. Respiratory causes of death were similar (n=3 vs n=2), suggesting this system was not responsible for the late deaths seen in the intervention group. Rates of withdrawal of care for neurological reasons were also similar (n=33 vs n=31). However, the main difference in causes of death can be seen in those who died from severe comorbidity (n=37 vs n=24) and also severe acute illness (n=14 vs n=4). Could the addition of vasopressin and a steroid have either imbalanced chronic severe disease or induced new acute severe illness? Or might it be more likely to simply be a chance finding? The alpha level of 0.05 states a 1-in-20 chance of a false positive finding, a result which may be more in keeping with the causes of death than any other obvious pathophysiological mechanism.

Questions have been raised as to whether adrenaline administration during cardiac arrest can help restore a coronary perfusion pressure, and thus a spontaneous cardiac output, but be cerebrally toxic, through the propagation of diminished cerebral blood flow and the development of microthrombi. Two randomised placebo-controlled trials, PARAMEDIC2[7] and PACA,[8] have compared adrenaline with placebo for resuscitation from cardiac arrest in the out-of-hospital setting. Both reported higher rates of ROSC, and numerically, but not statistically significantly, higher rates of survival, including with a good neurological outcome. A third trial[9] from Norway investigated the placement of an intravenous cannula with the administration of resuscitation drugs, including adrenaline, with the non placement of an IV cannula. Findings were similar to the adrenaline placebo controlled trials. Again, in this trial, there was no apparent evidence of an extra burden of brain injury in the intervention group.

As a non-catecholamine, vasopressin produces its effects through different receptors, mainly V2 for its vasopressor effect. Three trials have compared vasopressin with adrenaline and three have compared adrenaline plus vasopressin, with adrenaline. In a meta analysis[10] of these findings, no significant differences were found in any major outcome, including rate of ROSC (vasopressin vs adrenaline 27% vs 28%; RR, 1.05; 95% CI, 0.80 to 1.39) or survival to hospital discharge with a good neurological outcome.

Again, this suggests little effect, either therapeutic or toxic, from this drug in this setting.

Steroids have been used for blood pressure support in septic shock for many years, with this practice being shored up by the ADENAL[11] and APROCCHSS[12] trials, published in 2018. It is intriguing to compare the VAM-IHCA trial with the earlier Greek VSE trials. The populations included were similar. A notable difference between the groups is that the Danish study omitted post-arrest hydrocortisone for patients remaining in cardiogenic shock, while the VSE trials treated patients with 300 mg hydrocortisone daily until resolution of shock or until day 7. The VAM-IHCA trialists reasonably posited that the majority of benefit in the VSE trials came from the intra-arrest administration of methylprednisolone and vasopressin, and by separating intra- from post- arrest care, it would be possible to state more confidently that the intra-arrest bundle was effective on its own. This position was supported by a small three-centre American randomised controlled trial[13] in 50 post-cardiac arrest patients in shock, which failed to find evidence to support hydrocortisone in this subgroup of post arrest patients with shock.[1] However, it may be that the pleiotropic effects of hydrocortisone work separate, or parallel to, a permissive effect on the circulation, and that this bundle of vasopressin, methylprednisolone and hydrocortisone is required to be administered intact for a longer post arrest benefit to be seen. Perhaps the overt effect on blood pressure masked a covert effect of cerebral inflammation and neuro-apoptosis.

	VSE 1 (n = 299)	**VSE 2 *(n = 299)***	**VAM-IHCA *(n = 299)***
Year published	2009	2013	2021
Number analysed	100	268	501
Vasopressin dose	Total 100 IU	Total 100 IU	Total 80 IU
Post arrest hydrocortisone	300 mg daily	300 mg daily	Nil
Asystole as presenting rhythm	61%	67%	35%
Arrest in the ICU	31%	37%	8%
Time to study drug[14]	3 minutes	5 minutes	8 minutes

Table 4. Differences between the VSE1, VSE2 and VAM-IHCA trials

Where this sits in the body of evidence

Mentzelopoulos and colleagues performed a single-centre blinded, randomised controlled trial investigating the role of vasopressin, methylprednisolone and hydrocortisone in in-hospital cardiac arrest.[6] Both intervention and control groups received advanced life support as per the European Resuscitation Council Guidelines of 2005, including adrenaline 1mg intravenously with each resuscitation cycle. The intervention group received additional intra-arrest IV vasopressin 20 units per cycle (to a maximum of 100 IU) and a single dose of 40 mg methylprednisolone in the first resuscitation cycle, plus post arrest hydrocortisone 300 mg/day for those remaining in a state of shock. The control group received matching saline placebo. 100 consecutive patients were included. 46% of the cardiac arrests occurred in medical or surgical wards, 31% in the ICU and 18% in the Emergency Department and 5% in operating theatres. 61% had an initial rhythm of asystole and 25 pulseless electrical activity. Both primary endpoints, the rate of ROSC (81% vs 52%; P=0.003) and survival to hospital discharge (19% vs 4%; P=0.02) were higher in the intervention group.

The VSE 2[5] trial was the 2nd trial by Mentzelopolous and colleagues investigating the combination of vasopressin, methylprednisolone and hydrocortisone in cardiac arrest management. This follow-up trial was completed in three Greek centres and randomised 268 consecutive patients with cardiac arrest to the same interventions as described in the first trial by this group. 130 were randomised to the VSE group, and 138 to the control group. The approximate mean age of participants was 63 years and 68% were male. Prior to the cardiac arrest, 42% were suffering from hypotension, 20% had myocardial ischaemia or an infarction, and 35% had respiratory depression or failure. 69% of cardiac arrests occurred in either the medical/surgical ward setting or in the ICU. Most arrests were non-shockable; either asystole (67%) or pulseless electrical activity (16%). ROSC was achieved more often in the intervention group, 83.9% vs 65.9%; OR, 2.98; 95% CI, 1.39 to 6.40; P = 0.005. Similarly, patients in the intervention group had higher rates of survival to hospital discharge with a CPC score of 1 or 2; 13.9% vs 5.1%; OR, 3.28; 95% CI, 1.17 to 9.20; P = 0.02. A similar finding of improved CPC score 1 to 2 in those with post ROSC shock treated with hydrocortisone was also seen. Those in the vasopressin group had shorter cardiac arrests, higher mean arterial blood pressures and less organ dysfunction post arrest.

An individual patient data meta analysis[14] was performed by the trial groups behind both VAM-IHCA and the two VSE trials shortly after publication of VAM-IHCA. Just these three trials meet the inclusion criteria for in-hospital randomized controlled trials comparing vasopressin and glucocorticoids to placebo during cardiac arrest. All 3 trials were judged to have a low risk of bias for all outcomes. The three trials totalled 869 patients. There was moderate certainty in the primary finding that the combination of

vasopressin and methylprednisolone improved rates of ROSC (OR, 2.09; 95% CI, 1.54 to 2.84). Given the relatively low numbers of patients involved there was low certainty for medium term estimates of survival at discharge (OR,1.39; 95% CI, 0.90 to 2.14) and favourable neurological outcome (OR,1.64; 95% CI, 0.99 to 2.72).

Donnino and colleagues conducted an American three-centre, double-blind, randomised, placebo-controlled trial[13] investigating hydrocortisone in 50 patients with post ROSC shock after either in-hospital or out-of-hospital cardiac arrest. A shock state was defined as the requirement for a vasopressor infusion for at least one hour post ROSC. Patients in the intervention group received hydrocortisone 100 mg intravenously every 8 hours for up to 1 week or 24 hours after shock reversal. 25 patients were randomised to each group. Almost all patients (n=48) were recruited at a single site. The mean age of participants was 69 years and 66% were male. 76% had suffered an out-of-hospital cardiac arrest. The primary outcome, time to shock reversal, was similar between the hydrocortisone and control groups (HR, 0.83; 95 % CI: 0.40 to 1.75; P = 0.63). Secondary outcomes were also consistent with this: shock reversal, 52% vs. 60%, P=0.78; good neurological outcome (24% vs. 32%, P = 0.75 and survival to discharge, 28% vs 36%; P=0.76, respectively).

Should the combination of vasopressin and methylprednisolone be used in the resuscitation of in-hospital cardiac arrest?

Not at present. Rates of return of spontaneous circulation are improved, but longer term outcomes are not.

References

1. Welbourn C, Efstathiou N. How does the length of cardiopulmonary resuscitation affect brain damage in patients surviving cardiac arrest? A systematic review. Scand J Trauma Resusc Emerg Med 2018;26(1):77

2. Andersen LW, Holmberg MJ, Berg KM, Donnino MW, Granfeldt A. In-Hospital Cardiac Arrest. JAMA 2019;321(12):1200–10

3. Wongtanasarasin W, Krintratun S. Clinical benefits of corticosteroid administration during adult cardiopulmonary resuscitation: A systematic review and meta-analysis. World J Crit Care Med 2021;10(5):290–300

4. Lundin A, Djärv T, Engdahl J, et al. Drug therapy in cardiac arrest: a review of the literature. Eur Heart J - Cardiovasc Pharmacother 2016;2(1):54–75

5. Mentzelopoulos SD, Malachias S, Chamos C, et al. Vasopressin, Steroids, and Epinephrine and Neurologically Favorable Survival After In-Hospital Cardiac Arrest: A Randomized Clinical Trial. JAMA 2013;310(3):270–9

6. Mentzelopoulos SD, Zakynthinos SG, Tzoufi M, et al. Vasopressin, Epinephrine, and Corticosteroids for In-Hospital Cardiac Arrest. Arch Intern Med 2009;169(1):15–24

7. Perkins GD, Ji C, Deakin CD, et al. A randomized trial of epinephrine in out-of-hospital cardiac arrest. N Engl J Med 2018;379(8):711–21

8. Jacobs IG, Finn JC, Jelinek GA, Oxer HF, Thompson PL. Effect of adrenaline on survival in out-of-hospital cardiac arrest: a randomised double-blind placebo-controlled trial. Resuscitation 2011;82(9):1138–43

9. Olasveengen TM, Sunde K, Brunborg C, Thowsen J, Steen PA, Wik L. Intravenous drug administration during out-of-hospital cardiac arrest: a randomized trial. JAMA 2009;302(20):2222–9

10. Holmberg MJ, Issa MS, Moskowitz A, et al. Vasopressors during adult cardiac arrest: a systematic review and meta-analysis. Resuscitation 2019;139:106–21

11. Venkatesh B, Finfer S, Cohen J, et al. Adjunctive Glucocorticoid Therapy in Patients with Septic Shock. N Engl J Med 2018;378:797–808

12. Annane D, Renault A, Brun-Buisson C, et al. Hydrocortisone plus Fludrocortisone for Adults with Septic Shock. N Engl J Med 2018;378(9):809–18

13. Donnino MW, Andersen LW, Berg KM, et al. Corticosteroid therapy in refractory shock following cardiac arrest: a randomized, double-blind, placebo-controlled, trial. Crit Care 2016;20(1):1–8

14. Holmberg MJ, Granfeldt A, Mentzelopoulos SD, Andersen LW. Vasopressin and glucocorticoids for in-hospital cardiac arrest: A systematic review and meta-analysis of individual participant data. Resuscitation 2022;171:48–56

COCA

Vallentin MF, Granfeldt A, Meilandt C, Povlsen AL, Sindberg B, Holmberg MJ et al. Effect of Intravenous or Intraosseous Calcium vs Saline on Return of Spontaneous Circulation in Adults With out-of-hospital cardiac arrest. A Randomized Clinical Trial. JAMA 2021;326(22):2068-2076

Introduction

Out-of-hospital cardiac arrest affects approximately 55 per 100,000 people in the United Kingdom every year, with a return of spontaneous circulation achieved in 30% of attempted resuscitations, although this may vary depending on the initial rhythm.[1] Survival rates to hospital discharge are disappointingly low, with only 9% of patients recovering after the initial arrest.[1] International data is strikingly similar, although geographical variations highlight global inequalities.[2] Survival rates have marginally improved over time; however, few effective treatments other than early cardiopulmonary resuscitation (CPR) and rapid defibrillation have proven outcome benefits.[2,3]

Various drug treatments have been historically used to attempt to improve outcomes, but evidence is extremely limited. Although adrenaline improves survival at day-30 post out-of-hospital cardiac arrest, it does not result in more survivors with a good neurological outcome.[4] Guidelines recommend primarily the use of adrenaline and antiarrhythmics for cardiac arrest, but in reality multiple other drugs continue to be administered.[5,6] Calcium is recommended in specific circumstances, such as hyperkalaemia, but is frequently given.[5,6]

Calcium is required for cardiac muscle contraction, and its administration causes increased myocardial and vascular smooth muscle contraction, leading to increased inotropy and vasoconstriction.[7] These effects may be beneficial in cardiac arrest; specifically, vasoconstriction may increase aortic diastolic pressure, augment coronary blood flow and improve the chances of return of spontaneous circulation. However, hypercalcaemia may conversely promote cardiac dysrhythmias. Calcium has previously been investigated in two small randomised trials in refractory pulseless electrical activity (PEA) and asystolic arrests.[8,9] Although there was no overall survival benefit, there was a potential improvement in resuscitation success.[8,9] The use of calcium in shockable rhythms is unknown. The COCA trial was designed to investigate the use of calcium during out-of-hospital cardiac arrest.

Synopsis

This placebo controlled, parallel group, double-blind, randomised trial, performed in an emergency medical services system in Denmark, compared the administration of calcium with placebo in patients with out-of-hospital cardiac arrest. Adult patients who had suffered an out-of-hospital cardiac arrest were eligible after they had received at least one dose of adrenaline. Patients were excluded if the cardiac arrest was due to trauma, they had received resuscitation from a medical unit not participating in the trial, they were pregnant or they had a clinical indication for the administration of calcium (hypocalcaemia or hyperkalaemia).

Patients were randomised in a 1:1 ratio in block sizes of 2,4 or 6, using a random number generator and stratified by emergency care unit stations. Patients randomised to the calcium group received a bolus of 5 mmol of calcium chloride, administered as a bolus either intravenously or via the intraosseous route, immediately after the first dose of adrenaline. A second dose was administered after the second dose of adrenaline. Patients in the placebo group received a saline bolus. All other aspects of cardiac arrest management generally adhered to European Resuscitation guidelines.

The primary outcome was a sustained return of spontaneous circulation, which was defined as spontaneous circulation with no further need for chest compressions for at least 20 minutes. Secondary outcomes were survival at 30 days and survival at 30 days with a favorable neurological outcome, which was defined as a score of 0 to 3 on the modified Rankin Scale. Data on quality of life were also recorded using the 5-dimensional, 5-level EuroQol score. Sequential organ failure assessment (SOFA) scores were serially recorded and data on vasopressor-free and ventilator-free days within the first week were collected.

An original sample size of 430 patients had initially been calculated; however, after a blinded review of event rate data after recruitment of 270 patients, due to a lower than expected event rate, the required number of patients was increased. The expected rate of return of spontaneous circulation in the calcium group was 27% and in the saline group was 18%. Using a x^2 test 674 patients were required to identify this 9% difference with 80% power at the 5% significance level.

Patients were analyzed according to their randomised assignment. The analyses only included patients who received the trial drug. Five predefined subgroup analyses were performed according to the initial rhythm, the timing of the drug administration, intravenous vs intraosseous administration, whether the cardiac arrest was witnessed, and whether bystander cardiopulmonary resuscitation was performed. These analyses

were considered as exploratory and hypothesis-generating. Bayesian analyses were conducted to supplement the primary frequentist analyses.

The trial was stopped by the data and safety monitoring committee after a 15-month period, in which a total 397 patients had been recruited. This was unblinded data from 383 patients. During the trial recruitment period, a total of 1221 patients had an out-of-hospital cardiac arrest. 566 patients were excluded, as they did not receive adrenaline. 57 met exclusion criteria and another 189 were excluded for other reasons. Subsequently, 397 patients were randomised (197 to the calcium group and 200 to the saline group). Six patients were later excluded as they had a traumatic cardiac arrest.

Of the 397 patients, 277 (70.1%) were men with a median age around 68 years. The majority of arrests occurred at home (81.6%), 58.6% were witnessed and CPR was commenced in 79.3% of patients. 51% of the cardiac arrests were asystolic, 24% pulseless electrical activity, 23% ventricular fibrillation and 2% ventricular tachycardia. Drug delivery was mainly via the intraosseous route (60%), while the median time to delivery was 17 mins. 73% of patients received two doses of trial drug. Patient baseline characteristics at randomization were largely similar, although more patients in the saline group had both bystander CPR (89% vs 82%) and a higher proportion of shockable rhythms (27% vs 22%).

The primary outcome, sustained return of spontaneous circulation, occurred in 37 patients (19%) in the calcium group and 53 patients (27%) in the saline group (RR, 0.72; 95% CI, 0.49 – 1.03; P = 0.09). The results for any return of spontaneous circulation, and return of spontaneous circulation at hospital arrival, were similar. There was no difference across any of the pre-defined subgroups.

For the secondary outcomes, 30 days survival occurred in 10 patients (5.2%) in the calcium group and 18 patients (9.1%) in the saline group (RR, 0.57; 95% CI, 0.27 – 1.18; P = 0.17). Survival at 30 days with a favorable neurological outcome occurred in 7 patients (3.6%) in the calcium group and 15 patients (7.6%) in the saline group (RR, 0.48; 95% CI, 0.20 – 1.12; P =0 .12). Again, there were no differences in the predefined subgroups. Survival at 90 days was similar to the 30-day results.

In terms of safety data, the first ionized calcium level after return of spontaneous circulation was higher in the calcium group {1.41 mmol/L (SD, 0.15 mmol/L)} compared with the saline group {1.17 mmol/L (SD, 0.07 mmol/L)} and remained higher for approximately 12 hours.

In the Bayesian analysis, the probability that calcium had a beneficial effect was 4% for return of spontaneous circulation, 6% for survival at 30 days, and 4% for survival with a favorable neurological outcome at 30 days.

Critique

Calcium is required for many physiological processes which are essential for life.[7] The effect of calcium on cardiac myocytes has been known since the accidental contamination of fluids in experiments by Ringer over 100 years ago.[10] Calcium plays a crucial role in cell contraction and relaxation, with positive inotropic and chronotropic effects on the myocardium and increased vascular resistance resulting in increased cardiac output and blood pressure.[11] The effects have been used to improve haemodynamics after cardiac surgery, although the haemodynamic outcomes may be temporary and inconsistent.[12] Nevertheless, the potential haemodynamic benefits of calcium have been postulated as a therapeutic intervention in cardiac arrest. Increased diastolic myocardial perfusion through increased blood pressure may be beneficial in restoring cardiac output.[13]

Conversely, the myocardial effects may potentiate cardiac arrhythmias, increase myocardial oxygen demand and has been associated with myocardial hypercontraction or stone heart phenomenon.[12,13] Previous small randomised trials in refractory asystolic and pulseless electrical activity cardiac arrest have produced mixed results, but neither trial was large enough to make significant conclusions.[8,9] The COCA trial, therefore, had a physiological rational and investigated an important clinical problem where therapeutics are significantly lacking.

The COCA trial ultimately did not show a difference in the primary outcome of a sustained return of spontaneous circulation. The trial is the largest randomised trial investigating a calcium bolus in out-of-hospital cardiac arrest patients. It was an impressive undertaking, randomising a large population of patients in this emergency setting with blinding. The vast majority of patients received at least one dose of the trial intervention, there were minimal withdrawals and no patients lost to follow up. Furthermore, the authors included both frequentist and Bayesian statistical analysis, which improves understanding of the results.

The trial was stopped early by the data and safety monitoring committee after examining available data on 383 patients. This trial termination occurred despite no pre-defined stopping criteria. At this stage, there were significantly less return of spontaneous circulation events in the calcium group (17% vs 27%), and the data suggested a significant signal of harm (RR, 0.64; 95% CI, 0.43 to 0.94). Prior to recommending early cessation of the trial, a further 14 patients were recruited. With

these patients included, the subsequent analysis for harm was no longer statistically significant (RR, 0.72; 95% CI, 0.49 – 1.03; P = 0.09). This raises the possibility that the trial had been stopped prematurely, certainly far short of the planned sample size and is therefore underpowered. However, return of circulation rates in the calcium group were well below rates reported in other out-of-hospital cardiac arrest groups.[13] In addition, the Bayesian analysis suggested that the probability that calcium had a beneficial effect (risk ratio >1.0) based on the data is 4% for return of spontaneous circulation. This highlights the usefulness of the Bayesian methodology in this setting as the results are reassuring that calcium is highly unlikely to be a useful intervention in all cause out-of-hospital arrests.

Whether calcium might be useful in specific circumstances or specific types of cardiac arrest remains unknown. It is still recommended for arrests where hypocalcaemia or hyperkalaemia is suspected.[5] The COCA trial recruited all out-of-hospital cardiac arrest patients, excluding patients where there might have been a specific indication. This still resulted in a mixture of shockable (VT / VF) and non-shockable (asystole / PEA) cardiac arrests. Expected outcome from these situations is clearly different.[1] While the return of spontaneous circulation was better in the shockable group, there was no signal of benefit with calcium administration. The subgroup analysis in PARAMEDIC2 trial suggested potential survival benefit mainly in the non-shockable arrest group.[4] This, perhaps, suggests that the addition of calcium, or any other agent with pro arrhythmogenic properties, to a shockable cardiac arrest is unlikely to improve outcome. Previous calcium studies had suggested a potential benefit only in PEA cardiac arrests, more specifically, in patients with prolonged QRS complexes, with no benefit in asystolic arrests.[8,9] There was no difference in the subgroup analysis in the COCA trial; however, a more specific selection criteria might identify a population who could benefit, albeit this would be extremely difficult in the setting of out-of-hospital arrests.

Finally, this trial provides good evidence that a bolus of calcium should not be routinely used in out-of-hospital cardiac arrest without a specific indication. In fact, the results dispel the notion that, even in circumstances where the outcome looks bleak, a therapeutic trial should be considered, as it could cause later harm. The trialists postulated that the administration of calcium may have caused high levels of calcium leading to cytosolic and mitochondrial calcium overload, leading to cardiac hypercontraction, or stone heart.[13] The ionised calcium levels were elevated in the intervention group, and hypercalcemia, particularly in severe cases, can cause decreased myocardial function and vasodilation. The calcium was also given as a rapid bolus, which could have exacerbated hypercalcaemia. Other cardiac arrest trials have administered pharmacological interventions over a slower period of time.[16] This raises the question as to whether a smaller and more slowly delivered dose of calcium, or an infusion, might

have been more appropriate. However, the results of the COCA trial are unlikely to generate enthusiasm for further research on calcium in out-of-hospital cardiac arrests and should end the ad hoc administration in current practice.

Where this sits in the body of evidence

In a prospective, randomised, blind trial in 90 patients with refractory PEA cardiac arrest, 48 patients were randomised to receive calcium, and 42 to receive saline placebo. Only patients who had received adrenaline and bicarbonate, and were refractory to therapy, were eligible. Eight of 48 who received calcium were resuscitated successfully, and two of 42 who received saline were resuscitated successfully ($P < 0.07$). A successful resuscitation was defined as presentation to hospital with a pulse. Patients with a QRS width less than 0.12 seconds did not respond to calcium. Of those with widened QRS or ischemic changes (N = 70), eight of 39 who received calcium, compared with one of 31 not receiving calcium, were successfully resuscitated ($P < 0.028$). Only one patient was discharged from the hospital alive.[8]

In a prospective, randomised, blinded trial, 73 patients with refractory asystole were randomised to calcium chloride or saline. Refractory asystole was defined as patients who had received adrenaline, bicarbonate, and remained in asystole. Only three of 39 patients in the calcium group versus one of 34 in the saline group had a return of circulation. ($P=0.37$). No patient who was resuscitated successfully in the field was discharged from the hospital alive.[9]

In a randomised, double-blind trial, 8014 patients with an out-of-hospital cardiac arrest in the United Kingdom were randomised to adrenaline (4015 patients) or saline placebo (3999 patients), along with standard care.[4] The primary outcome was the rate of survival at 30 days. Secondary outcomes included the rate of survival until hospital discharge with a favourable neurologic outcome. At 30 days, 130 patients (3.2%) in the adrenaline group and 94 (2.4%) in the placebo group were alive (unadjusted odds ratio for survival, 1.39; 95% CI, 1.06 to 1.82; $P=0.02$). There was no evidence of a significant difference in the proportion of patients who survived until hospital discharge with a favourable neurologic outcome (87 of 4007 patients [2.2%] vs. 74 of 3994 patients [1.9%]; unadjusted odds ratio, 1.18; 95% CI, 0.86 to 1.61). At the time of hospital discharge, severe neurologic impairment (a score of 4 or 5 on the modified Rankin scale) had occurred in more survivors in the adrenaline group than in the placebo group (39 of 126 patients [31.0%] vs. 16 of 90 patients [17.8%]).

In a double-blind, placebo-controlled, phase 2 randomized clinical trial, 1502 adults with VF/VT out-of-hospital cardiac arrest were randomised to receive either 45 mg of sodium nitrite (n = 500), 60 mg of sodium nitrite (n = 498), or placebo (n = 499). The trial drug

was given as a bolus by the paramedics as soon as possible during active resuscitation. The primary outcome was survival to hospital admission. Secondary outcomes included rates of return of circulation, rearrests, inotrope requirements, neurological and survival outcomes. Overall, 205 patients (41%) in the 45 mg of sodium nitrite group and 212 patients (43%) in the 60 mg of sodium nitrite group compared with 218 patients (44%) in the placebo group survived to hospital admission; the mean difference for the 45-mg dose vs placebo was -2.9% (1-sided 95% CI, -8.0% to ∞; P = .82) and the mean difference for the 60-mg dose vs placebo was -1.3% (1-sided 95% CI, -6.5% to ∞; P = .66). None of the 7 prespecified secondary outcomes were significantly different.[15]

Should we routinely administer calcium in patients with out-of-hospital cardiac arrest?

No. The findings of the COCA trial are clear – there is no signal of benefit, and quite likely harm, from the administration of calcium without a specific indication in this condition.

References

1. Perkins GD, Nolan JP, Soar J, Hawkes C, Wyllie J, Skellett S et al. Epidemiology of cardiac arrest Guidelines. ERC Guidelines 2021: https://cprguidelines.eu

2. Yan, S., Gan, Y., Jiang, N, Wang R, Chen Y, Luo Z et al. The global survival rate among adult out-of-hospital cardiac arrest patients who received cardiopulmonary resuscitation: a systematic review and meta-analysis. Crit Care 2020;24:61

3. Perkins GD, Travers AH, Berg RA, Castren M, Considine J, Escalante R et al. Adult basic life support and automated external defibrillation: 2015 international consensus on cardiopulmonary resuscitation and emergency cardiovascular care science with treatment recommendations. Resuscitation 2015;95:e43-e69

4. Perkins GD, Chen J, Deakin CD, Quinn T, Nolan JP, Scomparin C, et al. A Randomized Trial of Epinephrine in out-of-hospital cardiac arrest. N Engl J Med 2018; 379:711-721

5. Soar J, Böttiger BW, Carli P, Couper K, Deakin CD, Djärv T et al. European Resuscitation Council Guidelines 2021: adult advanced life support. Resuscitation 2021;161:115-151

6. Moskowitz A, Ross CE, Andersen LW, Grossestreuer AV, Berg KM & Donnino MW. American Heart Association's Get With The Guidelines–Resuscitation Investigators. Trends over time in drug administration during adult in-hospital cardiac arrest. Crit Care Med 2019;47(2):194-200

7. Aguilera IM, & Vaughan RS. Calcium and the anaesthetist. Anaesthesia 2000;55(8):779-90

8. Stueven HA, Thompson B, Aprahamian C, Tonsfeldt DJ, Kastenson EH. The effectiveness of calcium chloride in refractory electromechanical dissociation. Ann Emerg Med 1985;14(7):626-9

9. Stueven HA, Thompson B, Aprahamian C, Tonsfeldt DJ, Kastenson EH. Lack of effectiveness of calcium chloride in refractory asystole. Ann Emerg Med 1985;14(7):630-2

10. Ringer S. A further contribution regarding the influence of the different constituents of the blood on the contraction of the heart. J Physiol 1882; 4:9-42

11. Shapira N, Schaff HV, White RD & Pluth JR. Hemodynamic effects of calcium chloride injection following cardiopulmonary bypass: response to bolus injection and continuous infusion. Ann Thorac Surg 1984;37:133-140

12. Lomivorotov VV, Leonova EA, Belletti A, Shmyrev VA & Landoni G. Calcium Administration During Weaning From Cardiopulmonary Bypass: A Narrative Literature Review. J Cardiothorac Vasc Anesth 2020;34(1):235-244

13. Piper HM, Meuter K & Schäfer C. Cellular mechanisms of ischemia-reperfusion injury. Ann Thorac Surg 2003;75(2):S644-8

14. Royster RL, Butterworth JF, Prielipp RC, Robertie PG, Kon ND, Tucker WY, et al. A randomized, blinded, placebo-controlled evaluation of calcium chloride and epinephrine for inotropic support after emergence from cardiopulmonary bypass. Anesth Analg 1992;74(1):3-13

15. Kim F, Maynard C, Dezfulian C, Sayre M, Kudenchuk P, Rea T et al. Effect of out-of-hospital Sodium Nitrite on Survival to Hospital Admission After Cardiac Arrest: A Randomized Clinical Trial. JAMA 2021;325(2):138-145

CAPITAL CHILL

Le May M, Osborne C, Russo J, So D, Chong AY, Dick A, et al. Effect of Moderate vs Mild Therapeutic Hypothermia on Mortality and Neurologic Outcomes in Comatose Survivors of Out-of-Hospital Cardiac Arrest. The CAPITAL CHILL Randomized Clinical Trial. JAMA 2021;326(15):1494-1503

Introduction

Out-of-hospital cardiac arrest remains a significant burden of healthcare systems worldwide, with an estimated annual incidence of 30.0 to 97.1 individuals per 100,000 population and survival to hospital discharge or day 30 with a favourable neurological outcome of 2.8% to 18.2%.[1]

Numerous interventions have been tested to improve outcomes both during and after this frequently catastrophic event, including extracorporeal circulatory support,[2,3] antibiotics,[4] early angiography,[5] and steroids.[6] However, the largest evidence base exists for therapeutic hypothermia, an intervention which has over 60 years of experimental support.[7] This intervention has been shown to reduce the cerebral metabolic rate for oxygen, limit hypoxic-ischaemic cerebral injury and potentially, improve both survival and survival with good neurological outcome after both out-of-hospital and in-hospital cardiac arrest.[8] However, despite a strong theoretical rationale, the numerous trials on the subject do not overall appear to provide convincing evidence this approach is efficacous.[9] The majority of trials have used mild hypothermia (32°C to 34°C), forcing the question as to whether a lower temperature may be more beneficial.

Synopsis

CAPITAL CHILL was a Canadian, single-centre, blinded, stratified, parallel group, randomised controlled trial comparing hypothermia at 31°C with 34°C in survivors of out-of-hospital cardiac arrest. It recruited patients between 2013 and 2022.

Eligible patients were adults who remained comatose after being resuscitated from an out-of-hospital cardiac arrest of presumed cardiac aetiology. The main exclusion criteria comprised a poor premorbid state, including nursing home residency, an inability to perform activities of daily living or a life expectancy of under a year; intracranial bleed as the cause for the cardiac arrest; major bleeding with severe coagulopathy or a known coagulation disorder; and the coma being unrelated to the cardiac arrest.

Patients were randomised with the use of sealed, opaque, serially numbered envelopes, in block sizes of 4 or 6, and stratified by the initial cardiac rhythm being shockable or non-shockable. Patients, treating clinicians and follow up assessors were blinded, with only the bedside nurse aware of the group allocation to permit temperature control.

Hypothermia was commenced as soon as possible after return of a spontaneous circulation, with pre-hospital staff advised to commence cooling with ice packs. Once in hospital, all patients were recommended to undergo immediate coronary angiography. An endovascular cooling catheter (Zoll Quattro catheter) was placed in a femoral vein as quickly as was practical, either in the cardiac catheterization lab or in the ICU. Patients were cooled to their assigned temperature, which was maintained for 24 hours. Rewarming occurred at 0.25°C per hour until a temperature of 37°C was reached, which was then maintained until hour 72. A multidisciplinary team performed multimodal neuroprognostication and withdrawal of life-sustaining therapy according to a predetermined strategy.

The primary outcome was a composite of all-cause mortality or poor neurologic outcome at 180 days. Poor neurological outcome was defined as a Disability Rating Scale score of > 5. Based on an expected 50% incidence of death or a poor neurological outcome in those treated at 34°C, 340 patients were required to identify a 30% relative risk reduction in the primary outcome in the group treated at 31°C , with 80% power at the 5% significance level. This was increased to 360 to allow for an expected 3% crossover rate. 19 secondary outcomes were planned.

591 patients suffering an out-of-hospital cardiac arrest were screened and 389 randomised. 18 patients were withdrawn from the trial and 4 did not receive the allocated interventions. The primary analysis was performed on the population of patients both randomised and who received the assigned therapy. There were 184 and 183 patients in the 31 °C and 34 °C groups, respectively.

Groups were largely similar at baseline. The mean age of patients in the trial was 61 years, 19% were female, 84% received bystander cardiopulmonary resuscitation, 86% had an initial shockable rhythm, 37% had an ST elevation myocardial infarction and 42% required vasoactive support. The time from call to the emergency services to return of spontaneous circulation was 23 (IQR, 15 to 35) and 20 (14 to 31) minutes in the 31 °C and 34 °C groups, respectively. Starting temperatures were identical in both groups at the point of randomisation (35.2 °C). The time from randomisation to target temperature was 208 (IQR, 163-282) minutes in the 31 °C group and 120 (80-174) minutes in the 34 °C group. The two groups achieved their target temperatures, which were maintained for the planned 24 hour maintenance period. The 34°C group returned to normothermia (37°C) at approximately 38 hours and the 31°C group at 52 hours. 7 patients in each group were non-adherent to the study protocol. More patients in the 31 °C group required a permitted 3 °C increase in temperature due to unfavourable haemodynamic parameters (31 patients vs 10 patients).

There was no significant difference in the primary outcome, occurring in 48.4% of the 31°C group and 45.4% of the 34°C group; difference 3.0%; 95% CI, −7.2% to 13.2%; RR, 1.07; 95% CI, 0.86 to 1.33; P = 0.56. One of the 19 secondary outcomes reported a statistically significant between group difference, with the 31°C group having a 3 day longer median length of stay in the ICU [10 vs 7 days; difference (expressed in means) 1.4; 95% CI -1.2 to 4.1; P=0.004]. Mortality rates at 180 days were 43.5% and 41.0% in the 31°C and 34°C groups, respectively; RR, 1.06; 95%, 0.83 to 1.35; P=0.63. There were similar rates of survivors being discharged home, at 90.3% and 92.5% in the two groups, respectively.

Critique

CAPITAL CHILL is the first medium sized randomised controlled trial to investigate moderate hypothermia at 31°C for the treatment of comatose survivors of out-of-hospital cardiac arrest. It reported an inconclusive effect for the primary outcome, with a 95% confidence interval spanning a range between a 7% reduction to a 13% increase in the incidence of death or poor neurological outcome at 180 days with moderate hypothermia.

The trial has many strengths, including immediate coronary angiography and therapy, quick induction of hypothermia, including commencement pre-hospital, randomisation after the placement of the endovascular cooling device was placed and confirmed to work, and a 24 hour maintenance phase with a 48 hour rewarming and avoidance of fever phase. The internal validity of the trial appears high, with both groups quickly achieving their target temperatures and staying at these values for the designated durations. Neuroprognostication was blinded, was addressed in a multidisciplinary format and followed a predefined strategy.

Generalisability suffers slightly from this trial being single centre and run in a specialist cardiac institution. All patients routinely underwent immediate coronary angiography, a standard not widely achievable. A high proportion of patients received bystander CPR (85% and 83%, in the 31°C and 34°C groups, respectively) and also coronary intervention (56.3% and 58.7%, respectively).

The power calculation of the trial is interesting to consider. A 30% relative risk reduction (15% absolute risk reduction) could be considered optimistic to achieve. Despite there being just a sample size of 360 patients, with therefore a limited number of events, the pre-planned analysis included 19 secondary outcomes. With an alpha set at 0.05, one false positive result could be expected. Just one of the 19 secondary outcomes showed a between-group difference, with a median difference in length of ICU stay of 3 days, favouring the 34°C group. This significant effect did not carry through to median length

of hospital stay at 22 vs 20 days, in the 31°C and 34°C groups, respectively (difference in means, −0.4 days; 95% CI, −5.1 to 4.3).

Whilst there appears to be little difference in outcome in patients managed after out-of-hospital cardiac arrest at either 31°C or 34°C, this trial doesn't answer the question as to whether a colder temperature than 31°C might prove beneficial. A recent systematic review and meta analysis[10] included 4 randomised controlled trials[11–14] evaluating hypothermia of 31°C to 32°C. When compared with normothermia (37°C to 37.8°C), there was no significant effect on survival with good neurological recovery (OR, 1.30; 95% CI 0.73 to 2.30) or overall survival (OR, 1.27; 95% CI 0.70 to 2.32), although these results were of low certainty. Similar results were found when compared with hypothermia at 33°C to 34°C, for both survival with good neurological outcome (OR 0.97, 95% CI, 0.61 to 1.54) and overall survival (OR, 1.03; 95% CI, 0.64 to 1.68). Adverse events were noted to be more common at the colder temperature, especially arrhythmias. There are presently no randomised controlled trials investigating temperatures below 31°C.

The combination of an intravascular cooling catheter and an inflammatory state may promote thrombosis, while systemic hypothermia and unfractionated heparin administration would oppose this. The ultimate balance between these pro- and anti-thrombotic influences may lead to an unpredictable effect on the rate of spontaneous clot formation. All patients underwent systematic doppler ultrasound of the legs and abdomen on days 3 and 5. There was no difference in the rate of deep venous thrombosis (DVT) between the 31°C (11.4%) and 34°C (10.9%) groups (RR, 1.04; 95% CI, 0.59 to 1.86; P = 0.88). Interestingly, there was a higher rate of thrombosis in inferior vena cava in the 34°C (3.8% vs 7.7%; RR, 0.50; 95% CI, 0.21 to 1.20; P = 0.11). For comparison, in a pre-planned analysis of the PREVENT trial, investigating the addition of intermittent pneumatic compression devices to pharmacological prophylaxis for the prevention of DVT, the baseline rate of DVT was approximately 4% in both groups.[15]

While CAPITAL CHILL examines the effect of a colder "dose" of hypothermia, a larger magnitude of hypothermia can be delivered in other ways, including a prolonged duration, faster induction or slower rewarming. The speed to achieve the desired temperature was explored in the TTM2 chapter in this book. In CAPITAL CHILL, cooling was commenced in the field immediately post return of spontaneous circulation via the application of ice packs. In 10 trials evaluating the pre-hospital commencement of therapeutic hypothermia, there was no clear effect on either survival to hospital discharge (RR,1.01; 95%CI, 0.92 to 1.11) or survival to hospital discharge with a favorable neurologic outcome (RR,1.00; 95%CI, 0.90 to 1.11).[9] Equally, a single trial comparing 48 with 24 hours of hypothermia at 32°C to 34°C found no significant between group

difference in the primary outcome of a favourable neurological outcome at 6 months; 69% vs 64%; RR, 1.08; 95% CI, 0.93 to 1.25; P = 0.33.

There appears to be few obvious weaknesses in CAPITAL CHILL. A biologically plausible question was tested in a robust manner in a clinical setting providing high level care. Although the inconclusive nature of the result is compatible with both benefit and harm from moderate hypothermia, the point estimate does not suggest a major effect from moderate hypothermia when compared to mild hypothermia. When viewed in light of a preponderance of contemporary clinical trials not showing clear benefit from therapeutic hypothermia at temperature ranges between 32°C and 34°C, the body of evidence questions the efficacy of this intervention. An obvious effect of keeping the temperature low for 1 to 3 days post cardiac arrest is the avoidance of periods of fever during this time. It remains to be seen whether it is this avoidance of fever which is the therapeutic modifier, rather than the colder temperature of mild hypothermia. The TTM3 trial will help answer this in due course.

Where this sits in the body of evidence

In 2002, Bernard and colleagues reported the results of an Australian multi-centre, randomised, open-label trial investigating therapeutic hypothermia in 275 comatose patients who had survived an out-of-hospital cardiac arrest. Patients in the hypothermia group were managed at a temperature of 32°C to 34°C, which was maintained for 24 hours, followed by passive rewarming to normothermia over 8 hours. The primary outcome was a favourable neurological outcome at 6 months, defined as a Pittsburgh Cerebral-Performance category score of 1 (good recovery) or 2 (moderate disability). This occurred in 55% of the hypothermia group and 39% of the normothermia group (RR, 1.40; 95% CI, 1.08 to 1.81; P=0.009). Mortality at 6 months was also lower in the hypothermia group (41% vs 55%; RR, 0.74).

The HACA study randomised 275 patients after out-of-hospital cardiac arrest due to ventricular fibrillation or tachycardia, and unresponsive to voice after achieving ROSC, to therapeutic hypothermia or standard care. Therapeutic hypothermia (target 32 - 34°C) was maintained for 24 hours followed by 8 hours of passive rewarming. The primary endpoint of favourable neurological outcome was seen in 55% of the therapeutic hypothermia group and 39% in the normothermia group (RR, 1.40; 95% CI, 1.08 to 1.81). After adjustment for baseline imbalances, hypothermia was associated with reduced mortality (RR, 0.62; 95% CI, 0.36 to 0.95).

In a study of 1,359 patients with out-of-hospital cardiac arrest who achieved ROSC, participants were randomised to standard care or 2 L of intravenous saline at 4°C.[16] Intravenous cold saline decreased patient temperature by 1.2 to 1.3°C and reduced the

mean time to reach 34°C (P < 0.001). There was no difference in the primary outcome measure of survival to hospital discharge; in those with VF, cold saline group, 62.7% (95% CI, 57.0% to 68.0%) vs control group, 64.3% (95% CI, 58.6% to 69.5%) (P = 0.69); in those without VF; cold saline group, 19.2% (95% CI, 15.6% to 23.4%) vs control group, 16.3% (95% CI, 12.9% to 20.4%) (P = 0.30). There was no difference in neurological outcome. There was a higher incidence of rearrest during transport in the cold saline group (26% vs. 21%; P = 0.008).

The TTM trial compared in-hospital cooling to 33°C with 36°C in 950 patients who had suffered an out-of-hospital cardiac arrest (irrespective of rhythm) and had a Glasgow Coma Scale score < 8.[17] The cooling intervention lasted for 24 hours and temperature was controlled to < 37.5°C for 72 hours. Cooling could be achieved by intravenous ice cold fluids, application of ice packs or commercially available cooling devices. There was no difference in 180 day mortality; 50% in the 33°C group compared to 48% in the 36°C group (HR, 1.06; 95% CI, 0.89 to 1.28; P = 0.51). There was no difference in the combined secondary endpoint of death or poor neurological outcome at 180 days (RR, 1.04; 95% CI, 0.89 to 1.17; P = 0.67).

The THAPCA-IH trial randomised 329 children aged 38 weeks to 18 years to therapeutic hypothermia (33.0 ± 1.0°C for 48 hours followed by maintenance of normothermia up to 120 hours) or normothermia following in-hospital cardiac arrest (IHCA).[18] Patients were required to be within 6 hours of ROSC and dependant on mechanical ventilation. There was no significant difference in the primary outcome of favourable neurobehavioral score at 12 months between the two groups; 36% vs. 39% in the hypothermia and normothermia groups, respectively (RR, 0.92; 95% CI, 0.67 to 1.27; P = 0.63). The investigators intended to recruit 558 patients but the trial was terminated early following an interim analysis on the basis of futility.

The THAPCA-OH trial examined cooling after out-of-hospital cardiac arrest and recruited patients from 38 ICUs in the United States and Canada.[19] 295 children who remained comatose after out-of-hospital cardiac arrest were allocated to therapeutic hypothermia (33.0 ± 1.0°C) or therapeutic normothermia (36.75 ± 0.75°C). Treatment commenced within 6 hours of ROSC. In contrast to the THAPCA-IH trial, the children in this trial were older (median age 2 years), 52% had no pre-existing medical conditions and 72% had a respiratory cause for their cardiac arrest. Asystole was the initial rhythm in 58% of cases. There was no difference in the primary outcome measure of survival at 12 months with a favourable neurobehavioral score; hypothermia group, 20% vs normothermia group, 12% (RR, 1.54; 95% CI, 0.86 to 2.76; P = 0.14). There was no difference in survival at 12 months; 38% vs. 29% in the hypothermia and normothermia groups respectively (P = 0.13).

The RINSE trial compared standard care with intra-arrest cooling achieved by administration of cold intravenous saline (3°C) in patients who had suffered an out-of-hospital cardiac arrest.[20] The trial was terminated early after recruitment of 1198 of a planned 2512 patients, due to changes in in-hospital temperature targets following the publication of the TTM trial. The temperature on arrival to hospital was lower in the intra-arrest cooling group; 34.7 ± 1.2°C vs 35.4 ± 1.3°C (P < 0.001). There was no difference in the primary outcome measure of survival to hospital discharge; 10.2% vs 11.4% in the intra-arrest cooling and standard care groups, respectively (P = 0.51). The intra-arrest cooling group had increased duration between arrival of emergency medical services and achieving ROSC (22.6 min vs 20.0 min, P=0.01), increased rates of death at scene (50.8% vs 45.3%, P = 0.06) and fewer patients transported with ROSC (33.5% vs 39.1% P = 0.04).

In 2019, Lascarrou and colleagues reported the results of the French multi-centre, open-label, HYPERION trial, comparing therapeutic hypothermia at 33°C ± 0.5°C with normothermia at 37°C in 584 patients comatose patients after suffering an in-hospital cardiac arrest with a non-shockable rhythm.[21] Patients in the hypothermia group had a temperature of 33°C ± 0.5°C maintained for 24 hours, followed by gradual rewarming at a rate of 0.25 to 0.50°C per hour, to 36.5 to 37.5°C, which was maintained for 24 hours. Those in the normothermia group had their temperatures maintained at 37°C ± 0.5°C for 48 hours. Patients in the hypothermia group had a higher rate of survival with a CPC score of 1 (good cerebral performance or minor disability) or 2 (moderate disability), 10.2% vs 5.7% (difference, 4.5%; 95% CI, 0.1 to 8.9; P=0.04). 90-day mortality was similar in both groups, 81.3% and 83.2%, in the hypothermia and normothermia groups, respectively (difference, −1.9%; 95% CI, −8.0 to 4.3).

The international, open-label, assessment blinded, randomised controlled TTM2 trial[22] compared hypothermia (33 °C) with normothermia (37.5 °C) in 1850 comatose survivors of out-of-hospital cardiac arrest. Groups were similar at baseline and excellent temperature separation was achieved. There was little difference in the primary outcome of death at 6 months, which occurred in 50% of those assigned to hypothermia and 48% of those assigned to normothermia (RR, 1.04; 95% CI, 0.94 to 1.14; P = 0.37). Functional outcomes were also similar at 6 months. Patients in the hypothermia group suffered more episodes of arrhythmias with haemodynamic compromise (24% vs 17%, P<0.001).

In February 2022, Bělohlávek and colleagues reported the results of the single-centre randomised controlled Prague Out-of-Hospital Cardiac Arrest study, investigating a package of interventions including mechanical chest compression, nasal cooling, intra-arrest transport, and immediate coronary angiography and intervention in patients

suffering refractory out-of-hospital cardiac arrest.[3] The control group received standard care. Although the trial was stopped early for futility after recruitment of 264 patients, there was numerically a large difference in the primary outcome of survival at 6 months with good neurological recovery; eCPR group vs control, 31.5% vs 22.0% (difference 9.5%; 95% CI, −1.3 to 20.1%; P=0.09). The secondary outcomes were coherent with the primary outcome, with a significant increase in survival at 30 days with good neurological recovery (30.6% vs 18.2%; difference, 12.4%; 95% CI, 1.9 to 22.7; P=0.02) and cardiac recovery at 30 days (43.5% vs 34.1%; difference 9.4%; 95% CI, −2.5 to 21%; P=0.12).

Following the publication of the TTM2 trial in June 2021, The International Liaison Committee on Resuscitation Advanced Life Support Task Force produced an updated systematic review and meta analysis on temperature management in comatose adults following cardiac arrest.[9] Six trials were included in a meta analysis comparing a target temperature range of 32 to 34°C with normothermia, usually with the avoidance of pyrexias. The induction of hypothermia at a target of 32 to 34°C did not result in an improvement in survival at 90 to 180 days (RR, 1.08; 95% CI, 0.89 to 1.30) or a favorable neurologic outcome, again at 90 to 180 days (RR, 1.21; 95%CI, 0.91 to 1.61).

Laurent and colleagues completed a small two-centre French randomised controlled trial in 61 comatose adult survivors of out-of-hospital cardiac arrest targeting the combined pathologies of post cardiac arrest syndrome and hypoxic ischaemia-encephalopathy.[11] They compared 3 strategies – (1) isovolumic high-volume hemofiltration, set at 200 ml/kg/h over 8 h (n=20) (2) isovolumic high-volume hemofiltration combined with therapeutic hypothermia, targeting 32°C for 24 hours (n=22), and (3) standard care (n=19). Groups were similar at baseline, with the exception that the hemofiltration group had a longer median period of cardiac arrest than the other two groups (25 minutes versus 14 and 16 minutes). Hypothermia was induced with large volumes of intravenous cold saline, at up to 12.5 l/hr. There was no significant difference in 6 month survival rates between the three groups: 32% in the HF+HT group, 45% in the HF group, and 21% in the control group (p = 0.28).

Should we induce moderate hypothermia at 31°C rather than mild hypothermia at 34 °C in comatose survivors of out-of-hospital cardiac arrest?

Probably not. Although CAPITAL CHILL compares two different levels of hypothermia, it is arguably trumped by the much larger TTM2 trial, showing no major difference in outcomes when normothermia is compared with hypothermia in this setting.

References

1. Kiguchi T, Okubo M, Nishiyama C, et al. Out-of-hospital cardiac arrest across the World: First report from the International Liaison Committee on Resuscitation (ILCOR). Resuscitation 2020;152:39–49.

2. Yannopoulos D, Bartos J, Raveendran G, et al. Advanced reperfusion strategies for patients with out-of-hospital cardiac arrest and refractory ventricular fibrillation (ARREST): a phase 2, single centre, open-label, randomised controlled trial. The lancet 2020;396(10265):1807–16.

3. Belohlavek J, Smalcova J, Rob D, et al. Effect of Intra-arrest Transport, Extracorporeal Cardiopulmonary Resuscitation, and Immediate Invasive Assessment and Treatment on Functional Neurologic Outcome in Refractory Out-of-Hospital Cardiac Arrest: A Randomized Clinical Trial. JAMA 2022;327(8):737–47.

4. François B, Cariou A, Clere-Jehl R, et al. Prevention of early ventilator-associated pneumonia after cardiac arrest. N Engl J Med 2019;381(19):1831–42.

5. Lemkes JS, Janssens GN, van der Hoeven NW, et al. Coronary angiography after cardiac arrest without ST-segment elevation. N Engl J Med 2019;380(15):1397–407.

6. Donnino MW, Andersen LW, Berg KM, et al. Corticosteroid therapy in refractory shock following cardiac arrest: a randomized, double-blind, placebo-controlled, trial. Crit Care 2016;20(1):1–8.

7. Benson DW, WILLIAMS JR GR, SPENCER FC, Yates AJ. The use of hypothermia after cardiac arrest. Anesth Analg 1959;38(6):423–8.

8. Hakim SM, Ammar MA, Reyad MS. Effect of therapeutic hypothermia on survival and neurological outcome in adults suffering cardiac arrest: a systematic review and meta-analysis. Minerva Anestesiol 2018;84(6):720–30.

9. Granfeldt A, Holmberg MJ, Nolan JP, et al. Targeted temperature management in adult cardiac arrest: Systematic review and meta-analysis. Resuscitation 2021;167:160–72.

10. Fernando SM, Di Santo P, Sadeghirad B, et al. Targeted temperature management following out-of-hospital cardiac arrest: a systematic review and network meta-analysis of temperature targets. Intensive Care Med 2021;47(10):1078–88.

11. Laurent I, Adrie C, Vinsonneau C, et al. High-volume hemofiltration after out-of-hospital cardiac arrest: a randomized study. J Am Coll Cardiol 2005;46(3):432–7.

12. Le May M, Osborne C, Russo J, et al. Effect of moderate vs mild therapeutic hypothermia on mortality and neurologic outcomes in comatose survivors of out-of-hospital cardiac arrest: the CAPITAL CHILL randomized clinical trial. JAMA 2021;326(15):1494–503.

13. Lopez-de-Sa E, Rey JR, Armada E, et al. Hypothermia in comatose survivors from out-of-hospital cardiac arrest: pilot trial comparing 2 levels of target temperature. Circulation 2012;126(24):2826–33.

14. Lopez-de-Sa E, Juarez M, Armada E, et al. A multicentre randomized pilot trial on the effectiveness of different levels of cooling in comatose survivors of out-of-hospital cardiac arrest: the FROST-I trial. Intensive Care Med 2018;44(11):1807–15.

15. Arabi YM, Al-Hameed F, Burns KE, et al. Adjunctive intermittent pneumatic compression for venous thromboprophylaxis. N Engl J Med 2019;380(14):1305–15.

16. Kim F, Nichol G, Maynard C, et al. Effect of prehospital induction of mild hypothermia on survival and neurological status among adults with cardiac arrest: a randomized clinical trial. J Am Med Assoc 2014;311(1):45–52.

17. Nielsen N, Wetterslev J, Cronberg T, et al. Targeted temperature management at 33 C versus 36 C after cardiac arrest. N Engl J Med 2013;369(23):2197–206.

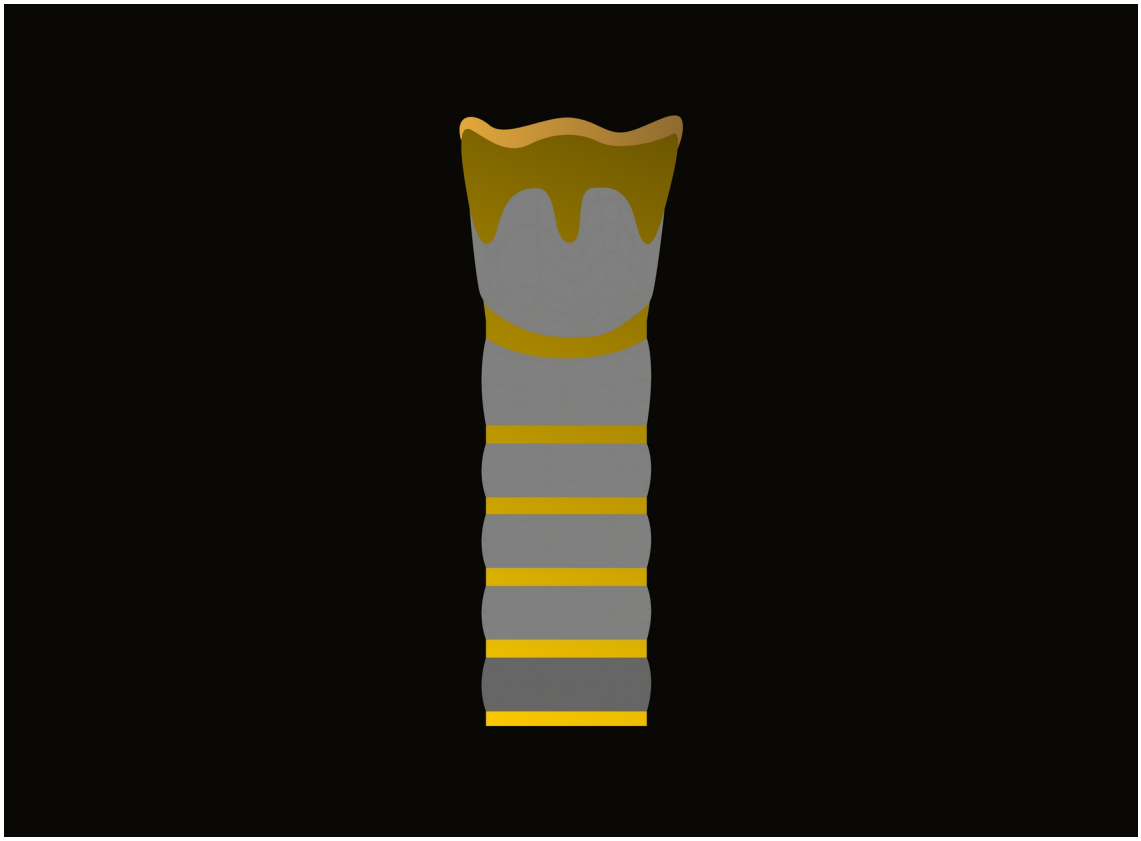
18. Moler FW, Silverstein FS, Holubkov R, et al. Therapeutic hypothermia after in-hospital cardiac arrest in children. N Engl J Med 2017;376(4):318–29.

19. Moler FW, Silverstein FS, Holubkov R, et al. Therapeutic hypothermia after out-of-hospital cardiac arrest in children. N Engl J Med 2015;372(20):1898–908.

20. Bernard SA, Smith K, Finn J, et al. Induction of therapeutic hypothermia during out-of-hospital cardiac arrest using a rapid infusion of cold saline: the RINSE trial (rapid infusion of cold normal saline). Circulation 2016;134(11):797–805.

21. Lascarrou J-B, Merdji H, Le Gouge A, et al. Targeted temperature management for cardiac arrest with nonshockable rhythm. N Engl J Med 2019;381(24):2327–37.

22. Dankiewicz J, Cronberg T, Lilja G, et al. Hypothermia versus normothermia after out-of-hospital cardiac arrest. N Engl J Med 2021;384(24):2283–94.



Airway Trials

The Bougie Study

Driver BE, Semler MW, Self WH, Ginde AA, Trent SA, Gandotra S et al. Effect of Use of a Bougie vs Endotracheal Tube with Stylet on Successful Intubation on the First Attempt Among Critically Ill Patients Undergoing Tracheal Intubation. A Randomized Clinical Trial. JAMA 2021;326(24):248-97

Introduction

Intubation is frequently required in critically ill patients. These urgent or emergency intubations can be more challenging, with reported difficult intubation rates up to 13%.[1] The 4th National Audit Project (NAP4) identified critical care and emergency medicine as particular areas for concern, with the consequences of a catastrophic airway event being around 60-fold higher in the intensive care.[2] Critically ill patients are often not fasted and have reduced physiological reserve leading to increased rates of hypoxaemia, hypotension, arrhythmia and death.[3] Complications occur more frequently with repeated intubation attempts, highlighting the importance of first attempt success.[4] Optimising the chances of successful intubation requires multiple interventions, including patient, team and environmental factors. Guidelines are now specifically available for critically ill patients.[3] However, recommendations on actual first attempt intubations are less prescriptive, mentioning video or direct laryngoscopy ± bougie or stylet, suggesting these can be interchanged.

Bougie or stylet use is only recommended when the laryngeal opening is poorly seen (Grade 2b or 3a view). The recent French STYLETO trial suggests routine use of a stylet to guide the passage of the endotracheal tube is superior to the placement of the endotracheal tube without an adjunct.[5] The evidence base has further grown with the publication of the single centre BEAM trial. This found the use of a bougie was superior to use of a stylet in first attempt intubations, without increasing complications.[6] However, BEAM was a single-centre trial in an institution with a high level of experience and skill with a bougie, reducing the generalisability of this approach to other centres. The BOUGIE trial, therefore, was the multi-centre follow up to the BEAM trial, and sought to confirm if the use of a bougie was superior to use of a stylet in critically ill patients.

Synopsis

This multi-centre, open-label, randomised trial was performed in 15 sites (7 emergency departments and 8 intensive care units) in the United States. It

compared use of a bougie with use of a stylet for tracheal intubation of critically ill patients. Adult patients requiring intubation in the emergency department or intensive care, with planned use of sedation and a standard laryngoscope blade, were eligible. Patients were excluded if tracheal intubation was required before randomization was possible, or if the clinician decided that a bougie or stylet was either required or was contraindicated. Pregnant patients and prisoners were also excluded.

The trial was approved with a waiver of informed consent. Patients were randomised in a 1:1 ratio to bougie-assisted intubation or intubation with an endotracheal tube containing a stylet. For intubations assigned to the bougie group, clinicians were instructed to pass the bougie and have an assistant load the endotracheal tube. For stylet intubations, clinicians were instructed to use an endotracheal tube loaded onto a malleable stylet, a distal bend of between 25° to 35°. All other aspects of the intubation procedure were at the clinician's discretion, including drug administration, laryngoscope choice and subsequent intubation equipment in the event of a failed attempt. Training videos and in person training was provided prior to recruitment. A trained observer collected data on the outcome of the intubation, including number of attempts, time to intubation and oxygen saturations. The Cormack Lehane grade of intubation and presence of difficult intubation characteristics were recorded. Data was also collected on the experience of the clinician and occurrence of complications.

The primary outcome was successful intubation on the first attempt. This was defined as a single insertion of the laryngoscope and subsequent single insertion of a bougie with single pass of the endotracheal tube or single insertion of the endotracheal tube with stylet. The secondary outcome was the incidence of hypoxaemia, defined as oxygen saturations less than 80% within 2 mins of intubation. Exploratory outcomes included time from induction to intubation. Complications, including airway injury, aspiration, oesophageal intubation, pneumothorax and cardiovascular compromise, were also recorded.

Assuming an 84% success rate on the first attempt in the stylet group, and anticipating less than 5% of patients would be missing data, 1106 patients were required to detect an absolute difference of 6% in the primary outcome between groups, with 80% power at a 2-sided α level of 0.05. The primary analysis was an unadjusted comparison of the primary outcome using the Chi squared test.

Further sensitivity analyses were performed investigating single laryngoscopy attempts for the primary outcome, crossover intubations, and intubations depending on the experience of the clinician. A further model also included use of a video laryngoscope, presence of difficult airway characteristics, and the Cormack-Lehane grade of glottic view.

Over a 2-year period, a total of 1558 patients requiring intubation were screened and 1477 patients fulfilled inclusion criteria. 371 of these met exclusion criteria, including 282 patients who required immediate intubation, while only 29 patients were excluded due to a clinician deeming a specific intubation technique was required. 1106 patients were randomised; 558 to the bougie group and 548 to the stylet group. Baseline characteristics were similar in the two groups. Approximately 60% of patients were male, 62% were of white ethnicity and the median body mass index was 26. The majority of intubations were for altered mental status (44.6%) and acute respiratory failure (31.5%), while 42.0% of patients had 1 or more difficult airway characteristics.

Almost two-thirds of patients were recruited in the emergency departments, with the most common clinician performing intubation being a resident physician (61.6%). In terms of experience, the clinicians had performed a median of 60 total intubations, with a median of 10 (IQR 4-20) intubations using a bougie. A video laryngoscope was most frequently used for intubation in both groups (75.7% bougie vs 73.8% stylet). The randomised intervention was used in 98% of intubation attempts.

There was no difference in the primary outcome measure of successful intubation on the first attempt; 80.4% vs 83.0% in the bougie and stylet groups, respectively (risk difference, −2.6%; 95% CI, −7.3 to 2.2; P = 0.27). Analysis defining successful intubation on the first attempt based only on the number of laryngoscope insertions (87.6% vs 88.6%) did not change the outcome. The odds of successful intubation on the first attempt did not differ significantly between groups in any of the prespecified subgroups, including operator experience, patients with difficult airway characteristics, or when a video laryngoscope was used.

For the secondary outcome, 58 patients (11.0%) in the bougie group experienced an oxygen saturation less than 80%, compared with 46 patients (8.8%) in the stylet group (absolute risk difference, 2.2%; 95% CI, −1.6 to 6.0).

Finally, in terms of exploratory outcomes, the median time interval from induction to tracheal intubation was faster in the stylet group at 112 seconds (IQR, 85-157) versus 124 seconds (IQR, 97-180) in the bougie group. Airway complications were identical, 1.8% in both groups, whilst there was minimal difference in pneumothorax rates. The bougie group had less cardiovascular collapse (12.2% versus 16.7%). 28 day mortality was 27.3% in the bougie group compared with 33.7% in the stylet group (difference, −6.4; 95% CI, −12.0 to −0.8).

Critique

Intubation guidelines recommend the use of either a stylet or a bougie in more difficult airway views or when intubation has proven difficult.[3] However, in critically ill patients, intubation is a high-risk procedure and repeated attempts at intubations are associated with harm.[4,7] Safe intubation on the first attempt is therefore desirable. The optimal strategy to achieve successful intubation is an important aim. This is, however, a complex intervention affected by patient, operator and situational factors. For improvements to be implemented, it is important to examine individual parts of this process and optimise each as effectively as possible. Stylet-assisted intubation has been shown to be superior to non-adjunct assisted intubation. In addition, the use of a bougie is potentially superior to stylet.[5,6] The Bougie trial was therefore an important and justified trial in the pursuit of an optimal intubating technique.

Ultimately, the results did not identify superiority of the bougie or stylet. This was a pragmatic trial designed to evaluate these adjuncts in real life practice. This was reflected in a failure rate of almost 20%, although this was a strict definition of failure, with other trials using the number of passes of the laryngoscope blade to determine failure. This failure rate was similar to the results of the STYLETO trial, but significantly higher than the 4% failure rate of the bougie group in the BEAM trial.[5,6] Intubations are difficult in critically ill patients, but if higher success rates are feasible, clinical trials of this nature should attempt to achieve the highest success rates possible.

There were significant differences between the BOUGIE and BEAM trials. The BEAM study was performed in a single centre with clinicians experienced and highly trained in the use of a bougie for intubations. The majority of centres in the BOUGIE trial rarely used a bougie for first attempts or only sometimes in a rescue situation. Although some training was provided, it is questionable whether the

clinicians were competent with a device that they had rarely used. The median number of intubations previously performed was just 60, with a median number of experiences with a bougie being just ten (IQR 4-20). The process of learning manual skills has previously been examined. Anaesthesia residents averaged around 60 intubations prior to achieving a 90% success rate in intubations (in theatre conditions). Even after 80 intubations, 18% still required assistance.[8] Obviously, learning curves vary between individuals but it is likely that a significant number of clinicians performing the intubations in the BOUGIE trial were inexperienced, particularly with the use of a bougie. In other institutions, routine practice is for more experienced or anaesthetic staff to intubate critically unwell patients.[7] An airway device is unlikely to improve performance unless the operator is skilled in its use. Furthermore, it is more likely that an attempt with an unfamiliar device is abandoned earlier if difficulty is experienced. The trialists did perform a sensitivity analysis accounting for experience with bougie-assisted intubations. This did not show a significant difference in performance, and may be explained by the smaller number of clinicians in this analysis or perhaps by the fact that the bougie was still not well integrated into the institution's intubation processes. A longer run-in time with bougie intubations, and perhaps a standardised approach to each intubation, prior to commencing the trial at each institution might in retrospect have improved the quality of the trial and eliminated some of the resulting confounders.

The sensitivity analysis interestingly did not show a difference in intubations that were graded as difficult. Difficult intubations were classified by airway characteristics (obesity, body fluid obscuring the glottis, cervical spine immobilization, and facial trauma) and also by grade of glottic view (although this was Cormack Lehane grade 2-4 rather than 3-4).[9] Airway management guidelines recommend the use of a bougie or stylet in difficult (grade 2b to 3) intubations, a recommendation which is not supported by the results of this trial.

Finally, the use of video laryngoscopy was around 75% in this trial. This was similar to the BEAM trial. However, screen use in the BOUGIE trial was almost universal, while despite using a video laryngoscope, screens were only used in around 45% of intubations in the BEAM trial. These usage rates are significantly higher than in other countries.[7] A recent Cochrane review concluded that video laryngoscopes improve the glottic view, but that there was limited evidence that the number of intubation attempts or the incidence of hypoxia or respiratory

complications were reduced. Nevertheless, they are still recommended in difficult airway guidelines.[10] Success rates in the BOUGIE trial were higher with use of a video laryngoscope than with direct laryngoscopy. This may again suggest that clinicians had limited experience, as the learning curve for video laryngoscopy may be more favourable.[1] The use of video laryngoscopy did not modify the effect of a bougie on successful intubation, but perhaps the results suggest video laryngoscopes may be part of a package of measures to improve first pass intubations and ultimately benefit patient care.

Where this sits in the body of evidence

In a multi-centre trial conducted over six months in 32 intensive care units, 999 patients were randomised to intubation with tracheal tube alone or with the use of a stylet.[5] The primary outcome was the first attempt success rate, while secondary outcomes included hypoxaemia, cardiovascular collapse, reported difficult intubation, aspiration or death. First-attempt intubation success occurred in 392 patients (78.2%) in the stylet group compared to 356 (71.5%) in the unassisted tracheal tube group (absolute risk difference, 6.7; 95% CI, 1.4 to 12.1; P = 0.01). There were no differences in complication rates, 38.7% in the stylet group and 40.2% in the unassisted tracheal tube group. Serious adverse events were similar between groups (4% stylet versus 3.6% unassisted tracheal tube). The trialists concluded that use of a stylet improves first intubation attempts.

In a single centre, open-label, randomised control trial conducted over 12 months in the emergency department of a tertiary medical centre, 757 adult patients requiring intubation were randomised to an initial intubation attempt assisted with a bougie or with an endotracheal tube with stylet.[6] The primary outcome was intubation success at the first attempt in predefined difficult airways. Secondary outcomes were success in all patients, success without hypoxaemia, duration of attempt and avoidance of oesophageal intubations. Among the 380 patients with at least 1 difficult airway characteristic, first-attempt intubation success was higher in the bougie group (96%) than in the stylet group (82%) (absolute between-group difference, 14%; 95% CI, 8% to 20%). The success rate continued to be higher (98% vs 87%) when all patients were analysed. There were no differences in duration of intubation or complication rates.

Can a bougie and a stylet be considered similarly clinically effective?

This is likely dependent on the degree of familiarity with both devices. The BOUGIE trial was in a setting of relatively inexperienced operators. It may be harder to extrapolate this to more expert groups and centres.

References

1. Natt BS, Malo J, Hypes CD, Sakles JC & Mosier JM. Strategies to improve first attempt success at intubation in critically ill patients. Br J Anaesthesia 2016;117,suppl 1: i60–i68

2. Cook TM, Woodall N, Harper J & Benger J. Major complications of airway management in the UK: results of the Fourth National Audit Project of the Royal College of Anaesthetists and the Difficult Airway Society. Part 2: intensive care and emergency departments. Br J Anaesth 2011;106:632–42

3. Higgs A, McGrath BA, Goddard C, Rangasami J, Suntharalingam G, Gale R et al. Guidelines for the management of tracheal intubation in critically ill adults. Br J Anaesth 2018;120(2):323-352

4. Mort TC. Emergency tracheal intubation: complications associated with repeated laryngoscopic attempts. Anesth Analg 2004;99:607–13

5. Jaber S, Rollé A, Godet T, Terzi N, Riu B, Asfar P, et al; STYLETO trial group. Effect of the use of an endotracheal tube and stylet versus an endotracheal tube alone on first-attempt intubation success: a multicentre, randomised clinical trial in 999 patients. Intensive Care Med 2021;47(6):653-664

6. Driver BE, Prekker ME, Klein LR, Reardon RF, Miner JR, Fagerstrom ET, et al. Effect of Use of a Bougie vs Endotracheal Tube and Stylet on First-Attempt Intubation Success Among Patients With Difficult Airways Undergoing Emergency Intubation: A Randomized Clinical Trial. JAMA 2018;319(21):2179-2189

7. Russotto V, Myatra SN, Laffey JG, Tassistro E, Antolini L, Baueret P al. Intubation Practices and Adverse Peri-intubation Events in Critically Ill Patients From 29 Countries. JAMA 2021;325(12):1164–1172

8. Konrad C, Schupfer G, Wietlisbach M & Gerber H. Learning Manual Skills in Anesthesiology Is There a Recommended Number of Cases for Anesthetic Procedures? Anesth Analg 1998;86(3):635-9

9. De Jong A, Molinari N, Terzi N, Mongardon N, Arnal JM, Guitton C et al. Early identification of patients at risk for difficult intubation in the intensive care unit: development and validation of the MACOCHA score in a multicenter cohort study. Am J Respr Crit Care Med 2013;187:832-839

10. Lewis SR, Butler AR, Parker J, Cook TM & Smith AF. Videolaryngoscopy versus direct laryngoscopy for adult patients requiring tracheal intubation. Cochrane Database Syst Rev. 2016;11CD011136

STYLETO

Jaber S, Rollé A, Godet T, Terzi N, Riu B, Asfar P, et al. Effect of the use of an endotracheal tube and stylet versus an endotracheal tube alone on first-attempt intubation success: a multicentre, randomised clinical trial in 999 patients. Intensive Care Med 2021;47(6):653-664

Introduction

The 4th National Audit Project (NAP4) highlighted the disproportionate incidence of major airway events in intensive care, with the consequences much more likely to lead to permanent harm or death than in anaesthesia.[1] This is not surprising given the often urgent need to secure the airway in a physiologically unstable patient. The INTUBE study showed that emergency intubation in critically ill patients, had a failure rate up to 20% and was associated with a complication rate up to 45.2%, consisting mainly of cardiovascular instability and severe hypoxaemia.[2] Complications including aspiration, hypoxaemia and cardiac arrest are associated with multiple attempts to secure the airway, with adverse outcomes increasing with successive attempts.[3,4]

First attempt successful intubation may reduce the incidence of complications and therefore strategies to improve intubation success and reduce complications should be a research priority.[5] Guidelines exist providing a structured approach to the management of the airway in the critically ill.[6] These highlight the patient, human and environmental factors involved, and recommend strategies for management of the difficult airway, whether anticipated or not. This guidance provides a number of suggestions for the difficult airway, including changes in positioning, laryngoscope and intubator, as well as use of either a bougie or stylet when the view of the larynx is poor (Cormack Lehane Grade 2b or 3). The evidence for the optimal strategy is lacking, particularly around the use of stylet or bougie, and indeed if these devices are useful in difficult airways, there maybe an argument for routine use in the critical care patient (a population with more difficult airways).

A previous study had suggested the use of a bougie for first attempt intubations could increase success rates and was superior to the stylet, although complications remained similar.[7] This trial was in the setting of experienced practitioners, in a single centre, where routine practice was to use the bougie. A subsequent larger multi-centre trial failed to replicate these results however.[8]

Rather than compare one adjunct over another, the STYLETO study investigated whether the stylet, a device recommended for difficult airways, could improve intubation success rates in the intensive care population. Given the high failure rates in this population, this was a worthwhile and justified trial.

Synopsis

This multi-center, open-label, randomised trial was performed in 32 ICUs in France. It compared stylet-assisted intubation with adjunct-free intubation, using the endotracheal tube alone, for the intubation of critically ill patients. Adult patients requiring intubation for mechanical ventilation in the ICU were eligible. Patients were excluded if they had suffered a cardiac arrest, or refused consent. Pregnant patients and protected patients were also excluded.

Participants were centrally randomised in a 1:1 ratio using a computer-generated sequence stratified by trial site to intubation using endotracheal tube with stylet or endotracheal tube alone. For the intubation procedure, all patients received general anaesthesia and a standard Macintosh laryngoscope was used. In the stylet group, the trachea was intubated using a endotracheal tube with stylet bent to 25° to 35° at the distal tip. All other aspects of the intubation procedure were at the clinician's discretion, including drug administration, laryngoscope choice and subsequent intubation equipment in the event of a failed attempt. In order to avoid extremes of practice the Montpellier intubation protocol was recommended.[9] The difficulty of intubation was assessed using the MACOCHA score.[10] A trained person who was not involved in the intubation collected data for periprocedural outcomes, including first-attempt intubation success and complications related to tracheal intubation. Immediately after the intubation the clinician performing the intubation reported the subjective level of difficulty, any injury and their level of experience. All other data was collected by from the medical records. The intubation was concealed from patients, research staff and the statistician.

The primary outcome was successful intubation on the first attempt. The secondary outcomes were complications suffered up to one hour after intubation. Complications included, hypoxaemia (defined as oxygen saturations less than 80% during intubation), hypotension (defined as systolic blood pressure less than 65 mm Hg or less than 90 mm Hg for thirty minutes despite fluid resuscitation or vasoactive requirement), cardiac arrest, incidence of arrhythmias or death.

Operator reported difficult or oesophageal intubation or aspiration were also recorded. Safety outcomes collected included traumatic injury, lowest saturations, highest required oxygen and positive end expiratory pressure (PEEP) up to 24 hours post intubation. In addition, ICU length of stay, ICU- and ventilator-free days, and 28 and 90 day mortality were also recorded.

Assuming a 70% success rate in the endotracheal tube only group on the first attempt, an 80% success rate in the stylet group, and anticipating that less than 10% of patients would be missing, 1040 patients would provide 95% power, at a 2-sided α level of 0.05, to detect an absolute between group difference of 10% in the primary outcome. The primary analysis was a modified intention-to-treat population (excluding patients randomised who did not met inclusion criteria or who were not intubated) using the Chi squared test.

Over a six-month period, 1626 patients fulfilled inclusion criteria and 430 of these met exclusion criteria. Of those, 122 patients were post arrest, 93 refused consent, 134 were previously enrolled, while 156 were not enrolled due to unavailability of research staff. Ultimately, 1040 patients were randomised; 522 to the stylet group and 518 to the endotracheal tube group. Subsequently, 41 patients did not complete the trial. Baseline characteristics were similar in the two groups; approximately 63% of patients were male, median SOFA score was 6.0 and the median body mass index was twenty-six. The majority of intubations were for altered mental status (25%) and acute respiratory failure (48%), while 23% of patients had a moderate or high risk of a difficult airway.

An anaesthetist was the intubator in almost 60% of cases, although this was a more junior clinician in around 43% of cases. A junior intensivist was involved in around one third of cases. In terms of experience, the clinicians had performed around 350 previous intubations.

There was a significant difference in the primary outcome measure of successful intubation on the first attempt; 78.2% in the stylet group vs 71.5% in the endotracheal tube group (absolute risk difference of 6.7%; 95% CI, 1.4 to 12.1; P = 0.01). The number needed to treat with a stylet to prevent one intubation failure was 14.8 (95% CI, 8.3 to 71.7). No additional effect was seen in subgroup analyses.

In terms of the secondary outcomes, 194 patients (38.7%) in the stylet group had at least one complication related to tracheal intubation, compared with 200 patients (40.2%) in the endotracheal tube group (absolute risk difference, −1.5; 95% CI, − 7.5 to 4.6; P=0.64). There was no significant difference regarding the incidence of serious adverse events (4.0% vs 3.6%).

Finally, in terms of safety outcomes, there were no significant between-group differences in lowest oxygen saturation, PEEP levels or oxygen requirements, nor in the number of invasive ventilatory-free days or mortality.

Critique

Intubation is a high-risk procedure in the ICU, with repeated attempted associated with harm.[2,3] Safe intubation without complications should be a priority, with the aim this will translate into better patient outcomes. Therefore, strategies to improve first attempt intubation are an important early step in the management of critically ill patients. Guidelines recommend the use of a bougie or stylet in the management of difficult airways but not necessarily for all airways.[6] The STYLETO trial introduced a simple and commonly used intervention into the complex airway management of critically ill patients. This was a well conducted trial which produced a clear answer - the use of a stylet improved first pass intubation in a mixed population of critically ill patients. The trial recruited from multiple centres, had minimal protocol violations and included clinicians with variable experience, all of which translates into results that can be easily generalised.

However, despite these impressive results, there are some considerations before implementing stylet use as a standard of care. The INTUBE investigators reported a real world first attempt success rate of 79.8%. This was similar to the first attempt success rate of the stylet group, but significantly higher than the endotracheal tube group.[2] The apparent improvement in the stylet group appears less significant if the results are on a par with standard care. There were, however, some differences in the populations; in particular, the STYLETO trial cohort had higher MACOCHA scores (indicating more difficult airways). In subgroup analysis, the use of a stylet failed to demonstrate benefit in obese patients or those with a difficult airway. Also, the clinicians were less experienced than those in the INTUBE study.[2] In fact in the STYLETO trial, 75% of the first attempts at tracheal intubation were performed by non-expert operators. Although this may be reflective of real-world practice, it does, perhaps, highlight that if higher success

rates are to be achieved, and patient outcomes improved, the reality is experience probably matters. Subgroup analysis did not show an effect of operator experience on first pass success but this was a small group. Given the low percentage of experienced clinicians, whether a stylet improves intubation attempts in expert hands also remains to be proven.

The choice of direct laryngoscopy with a standard Macintosh laryngoscope is possibly becoming less relevant to airway management today, particularly post COVID-19. The INTUBE study showed use of videolaryngoscopy in 17.1% of cases, while use in the BOUGIE trial was almost 75% of patient intubations were with a videolaryngoscope. Even rescue attempts with videolaryngocsopes was rare in the STYLETO trial.[2,8] Videolaryngoscopes improve the glottic view and are recommended in difficult airways but there is limited evidence on the effect of first pass intubations.[11] Stylets are frequently recommended for videolaryngoscopy with limited evidence; however, it is not possible to extrapolate the results of the STYLETO trial unless the videolaryngoscope was used for direct vision as was frequently the case in the BEAM trial.[7]

Finally, despite an improvement in first attempt intubations, there was surprisingly no difference in intubation times, but more importantly, the complication rates observed. The STYLETO trial recommended the Montpellier intubation protocol, which consists of a series of procedures in order to limit intubation complications. Compliance with this was generally good and similar in each group. Despite this, complications were around 40% in both groups, and was only slightly lower than the 45% reported in the INTUBE study[2] despite being under trial conditions. Up to 25% of patients suffered severe hypoxaemia or cardiovascular collapse. This further highlights the need for future research with the aim to not only improve first pass intubations but also reduce the rates of complications. The Montpellier protocol has been shown to reduce complications in a small phase two study; interestingly, the fluid bolus aspect (an intervention under investigation in the PREPARE II trial) and use of vasopressors had poor compliance rates in the STYLETO trial[12] This trial has not provided a definitive solution to the risks of intubation in critically ill patients; however, the results of the STYLETO trial, along with the BEAM and BOUGIE trials do highlight the potential benefits of first intubation attempts aided by bougie or stylet. Airway management is a complex intervention that requires more than the placement of

an endotracheal tube in the trachea to improve safety and ultimately patient outcomes.[7,8]

Where this sits in the body of evidence

In a single centre, open-label , randomised control trial conducted over 12 months in the emergency department of a tertiary medical centre, 757 adult patients requiring intubation were allocated to initial intubation attempt with bougie or endotracheal tube with stylet. The primary outcome was intubation success at the first attempt in predefined difficult airways. Secondary outcomes were success in all patients, success without hypoxaemia, duration of attempt and avoidance of oesophageal intubations. Among the 380 patients with at least 1 difficult airway characteristic, first-attempt intubation success was higher in the bougie group (96%) than in the stylet group (82%) (absolute between-group difference, 14%; 95% CI, 8% to 20%). The success rate continued to be higher (98% vs 87%) when all patients were analysed. There were no differences in duration of intubation or complication rates.[7]

In a multi-centre randomised control trial conducted over 2 years in seven emergency departments and eight ICUs in the United States, 1102 adults patients requiring intubation were randomised to an initial intubation attempt with bougie or stylet. The primary outcome was successful intubation on the first attempt. The secondary outcome was the incidence of severe hypoxemia, defined as a peripheral oxygen saturation of less than 80%. Successful intubation on the first attempt occurred in 447 patients (80.4%) in the bougie group and 453 patients (83.0%) in the stylet group (absolute risk difference, -2.6%; 95% CI, -7.3 to 2.2; P=0.27). There were no differences in the rates of hypoxaemia (11.0% vs 8.8%) or any safety outcomes.[8]

Should we use a stylet when intubating critically ill adults?

Maybe. The evidence supports the use of a bougie or stylet, but it is unclear whether one is superior over the other.

References

1. Cook TM, Woodall N, Harper J & Benger J. Major complications of airway management in the UK: results of the Fourth National Audit Project of the Royal College of Anaesthetists and the Difficult Airway Society. Part 2: intensive care and emergency departments. Br J Anaesth 2011;106: 632–42

2. Natt BS, Malo J, Hypes CD, Sakles JC & Mosier JM. Strategies to improve first attempt success at intubation in critically ill patients. Br J Anaesth 2016;117,suppl 1: i60–i68

3. Russotto V, Myatra SN, Laffey JG, Tassistro E, Antolini L, Baueret P al. Intubation Practices and Adverse Peri-intubation Events in Critically Ill Patients From 29 Countries. JAMA 2021;325(12):1164–1172

4. Mort TC. Emergency tracheal intubation: complications associated with repeated laryngoscopic attempts. Anesth Analg 2004;99:607–13

5. Sakles JC, Chiu S, Mosier J, Walker C, Stolz U. The importance of first pass success when performing orotracheal intubation in the emergency department. Acad Emerg Med 2013;20:71–8

6. De Jong A, Rolle A, Pensier J, Capdevila M, & Jaber S. First-attempt success is associated with fewer complications related to intubation in the intensive care unit. Intensive Care Med 2020;46:1278–1280

7. Higgs A, McGrath BA, Goddard C, Rangasami J, Suntharalingam G, Gale R et al. Guidelines for the management of tracheal intubation in critically ill adults. Br J Anaesth 2018;120(2):323-352

8. Driver BE, Prekker ME, Klein LR, Reardon RF, Miner JR, Fagerstrom ET, et al. Effect of Use of a Bougie vs Endotracheal Tube and Stylet on First-Attempt Intubation Success Among Patients With Difficult Airways Undergoing Emergency Intubation: A Randomized Clinical Trial. JAMA 2018;319(21):2179-2189

9. Driver BE, Semler MW, Self WH, Ginde AA, Trent SA, Gandotra S et al. Effect of Use of a Bougie vs Endotracheal Tube with Stylet on Successful Intubation on the First Attempt Among Critically Ill Patients Undergoing Tracheal Intubation. A Randomized Clinical Trial. JAMA 2021;326(24):2488-97

10. Jaber S, Jung B, Corne P, Sebbane M, Muller L, Chanques G, et al. An intervention to decrease complications related to endotracheal intubation in the intensive care unit: a prospective, multiple-center study. Intensive Care Med 2010;36:248–255

11. De Jong A, Molinari N, Terzi N, Mongardon N, Arnal JM, Guitton C et al. Early identification of patients at risk for difficult intubation in the intensive care unit: development and validation of the MACOCHA score in a multicenter cohort study. Am J Respr Crit Care Med 2013;187:832-839

12. Lewis SR, Butler AR, Parker J, Cook TM & Smith AF. Videolaryngoscopy versus direct laryngoscopy for adult patients requiring tracheal intubation. Cochrane Database Syst Rev. 2016;11CD011136

13. Russell DW, Casey JD, Gibbs KW, Dargin JM, Vonderhaar DJ, Joffe AM et al. PREPARE II Investigators. Protocol and statistical analysis plan for the PREventing cardiovascular collaPse with Administration of fluid REsuscitation during Induction and Intubation (PREPARE II) randomised clinical trial. BMJ Open 2020;10(9):e036671.

Respiratory Trials

REST

McNamee JJ, Gillies MA, Barrett NA, Perkins GD, Tunnicliffe W, et al. Effect of Lower Tidal Volume Ventilation Facilitated by Extracorporeal Carbon Dioxide Removal vs Standard Care Ventilation on 90-Day Mortality in Patients With Acute Hypoxemic Respiratory failure. JAMA 2021;326(11):1013-1023

Introduction

Whilst mechanical ventilation provides life-saving support for those with respiratory failure, it can impose an additional inflammatory insult on already injured lungs. Ventilator-induced lung injury can be induced via multiple interlinked processes, including volutrauma, barotrauma, atelectrauma, biotrauma, diaphragmatic dysfunction and oxygen toxicity. Ultra-low tidal volume ventilation is the use of tidal volumes of approximately 2-3 mL/kg predicted body weight (PBW), far below the usual 6 mL/kg PBW recommended for patients with acute respiratory distress syndrome (ARDS). By delivering a smaller tidal volume to poorly compliant, oedematous, injured lungs, the mechanical power required is lessened, and in theory, so too is the additional inflammatory injury induced by mechanical ventilation. The cost of this approach, however, is the retention of carbon dioxide and resulting acidosis.

Although the proportion of patients with respiratory failure who die from refractory hypoxaemia is low, at less than 20%,[1,2] the introduction of extra-corporeal respiratory support in parallel to mechanical ventilation, can improve survival for those with severe respiratory failure.[3] However, due to the high costs and expertise required, highly invasive extracorporeal support such as veno-venous- or veno-arterial extracorporeal membrane oxygenation (VV-ECMO or VA-ECMO), has limited availability. Extra-corporeal carbon dioxide removal ($ECCO_2R$) is another form of extra-corporeal respiratory support, which requires just a single large, double-lumen venous cannula, and is less invasive than ECMO. Could the additional of an $ECCO_2R$ machine facilitate the introduction of ultra-low tidal volume ventilation by eliminating the residual carbon dioxide load from the hypoventilation caused by such an approach?

Synopsis

The REST trial tested the hypothesis that in critically ill patients receiving invasive mechanical ventilation for acute hypoxaemic respiratory failure, $ECCO_2R$, with the aim of facilitating a reduction of tidal volumes from 6 mL/kg PBW to ≤ 3 mL/kg PBW, would reduce 90-day mortality by 9%, from 41% to 32%.[4]

This UK open-label, pragmatic, randomised controlled trial recruited patients in 51 centres between 2016 and 2019. Eligible patients were adults (> 16 years old) with early, within 48 hours of onset, acute moderate-to-severe hypoxaemic (PaO_2/FiO_2 < 150 mm Hg) respiratory failure receiving invasive mechanical ventilation. Exclusion criteria included a duration of invasive mechanical ventilation > 7 days, a contraindication to systemic heparin anticoagulation, respiratory failure due to pulmonary oedema from severe left ventricular failure or fluid overload, untreated pulmonary embolism, pleural effusion or pneumothorax. Randomisation was performed with a computer-based system, which was accessed via a central web-based or telephone system, and occurred in a 1:1 ratio to control or intervention groups, stratified by centre, and in variable block sizes of 4, 6 or 8.

The intervention consisted of $ECCO_2R$ plus ultra-low tidal volume ventilation. The Alung Hemolung-RAS VV- $ECCO_2R$ device (Alung® Technologies, Pittsburgh, USA) was used at all centres. It was interfaced via a 15.5F reinforced, dual lumen catheter placed percutaneously using the Seldinger technique with ultrasound guidance, preferentially into the right internal jugular vein or a femoral vein. The pump speed was set to obtain the maximal blood flow possible, usually 350 to 450 mL/min. The sweep gas flow was initially set to 1 L/min and was increased to 10 L/min to obtain the maximal carbon dioxide removal possible. Systemic unfractionated heparin was administered, targeting an APPT of 45 to 65 seconds, to prevent thrombosis in the extracorporeal circuit. Tidal volumes were gradually reduced towards 3 mL/kg PBW, targeting a Pplat ≤ 25 cmH_20 and an arterial pH ≥ 7.20. This was continued for at least 48 hours, at which point an assessment was made to determine whether the patient was suitable for commencement of $ECCO_2R$ weaning. The extracorporeal support was to be used for a maximum of 7 days.

The control group received standard lung protective ventilation, with a tidal volume of 6 mL/kg PBW and a target Pplat ≤ 30 cmH_2O. Both groups could receive additional therapies as necessary, including neuromuscular blocking drugs, inhaled pulmonary vasodilators, prone positioning or ECMO (requiring discontinuation of $ECCO_2R$). Airway pressure release ventilation and high frequency oscillatory ventilation were not permitted.

The primary outcome was all-cause mortality at day 90. Secondary outcomes included short-term indicators of internal validity (tidal volumes at day 2 and 3), medium terms markers of clinical efficacy (ventilator-free days at day 28, duration of invasive mechanical ventilation, ECMO requirement, mortality at day 28, safety events) and longer-term economic (Health and Social Care Service costs at 6 months and 1 year) and clinical endpoints (St George's Respiratory Questionnaire at 1 year, home oxygen

requirement at 6 months and 1 year, Post Traumatic Stress Syndrome Questionnaire at 1 year and Montreal Cognitive Assessment or AD8 Dementia Screening Interview at 1 year).

The expected effect size of the combination of $ECCO_2R$ and ultra-low tidal volume ventilation on 90 day mortality was 9%. This was based on the 9% mortality difference seen in the landmark ARDSnet ARMA trial, comparing tidal volumes of 6 mL/kg PBW with 12 mL/kg PBW in patients with ARDS. With an expected control group mortality of 41%, and predicted intervention group mortality of 32%, 1120 patients were required to identify this effect size with 90% power at the 5% significance level with a 2-sided test. An interim analysis was planned after the recruitment of 560 patients. There were no formal stopping rules. Results are presented as risk ratios.

The interim analysis was undertaken early during a pause for the investigation of a serious adverse event. Following this analysis, the data and safety monitoring committee recommended the termination of the trial based on futility.

7071 patients had been screened and 412 recruited. The most common reasons for exclusion from the trial were a contraindication to systemic anticoagulation, a predicted survival of less than 6 months, planned treatment withdrawals or limitations. 202 patients had been randomised to the interventional group and 210 to the control group. The groups were similar at baseline. Approximate combined values for the entire cohort were: median age 61 years; 65% male; 87% fully independent prior to trial recruitment; 86% had a respiratory pathology, 46% a diagnosis of sepsis; ARDS was present in approximately 61%, predominantly due to pneumonia (61%) or sepsis (48%); APACHE II score 20; SOFA score 10; neuromuscular blocking drugs 50%; prone positioning 11%; tidal volumes 6.3 mL/kg PBW and respiratory rate 24 breaths per minute; PEEP 10 cmH20; Pplat 26 cmH_20; driving pressure 15 cmH_20 and PaO_2/FiO_2 117 mm Hg.

92% of the intervention group received $ECCO_2R$ for a mean duration of 4 days. One patient in the control group received $ECCO_2R$. The mean tidal volume was significantly lower in the intervention group at day 2 (4.5 vs 6.5 mL/kg; mean difference, 2.0 mL/kg; 95% CI, 1.7 to 2.3)and at day 3 (4.4 vs 6.7 mL/kg; mean difference, 2.3 mL/kg; 95% CI, 2.0 to 2.7). Plateau pressures were similarly lower at days 2 and 4.

90 day mortality was 41.5% in the intervention group and 39.5% in the control group (RR, 1.05; 95% CI, 0.83 to 1.33; P=0.68). Patients in the intervention group had two fewer ventilator-free days by day 28 (7.1 vs 9.2; difference, -2.1; 95% CI, -3.8 to 0.03; P=0.02). There was no difference in the need for ECMO to day 7 (6% vs 3%; RR, 2.08; 95% CI 0.80 to 5.43; P=0.13), ICU length of stay (14 vs 13 days; P=0.13), hospital length of stay

(22 vs 18 days; P=0.65) or 28 day mortality (38% vs 36%, RR, 1.06; 95% CI, 0.82 to 1.37; P=0.64). More adverse (168 vs 61) and serious adverse events (70 vs 20) were reported in the intervention group. There were 10 reports of intracranial haemorrhage in the intervention group and 2 in the control group, and 6 versus 1 reports of serious extracranial bleeding, respectively. Longer term outcomes have not yet been presented.

Critique

REST was a well designed and excellently executed trial. It is presently the largest extracorporeal trial of respiratory support in the critically ill, a field which has little preceding evidence, making many aspects of the trial design difficult and based on inference and judgement from previous works.

The underlying premise of the REST trial was that ventilator induced lung injury could be reduced by decreasing tidal volumes from 6 mL/kg PBW to 3 mL/kg PBW, and thus clinical outcomes improved. To date, the results of mechanistic work looking at pulmonary and systemic inflammatory levels in REST have not yet been published. However, there is a small amount of available data to contest this premise. In the Xtravent study,[5] which also compared tidal volumes of 6 mL/kg PBW with 3 mL/kg BPW supported by $ECCO_2R$, there was no clear effect on the plasma levels of the inflammatory biomarkers TNF-a, IL-6, and IL-8. Similarly, a recent study in patients undergoing ultra-low tidal volume ventilation (≈ 3 mL/kg PBW) facilitated by ECMO also failed to show a reduction in lung inflammation.[6] It may also be possible to reduce tidal volumes to levels as low as 3 and 4 mL/kg PBW without the use of an $ECCO_2R$ machine. In a French prospective before-and-after study of 35 ARDS patients within 24 hours of ARDS diagnosis and with $PaO_2/FiO_2 \leq 150$ mm Hg, it was feasible to decrease tidal volumes from 6 mL/kg PBW to 4 mL/kg PBW without the use of $ECCO_2R$.[7] One third of patients developed a transient pH < 7.15. Overall, at 41%, the 28 day mortality of this cohort was similar to the hospital mortality of 40% of the moderate ARDS group (PaO_2/FiO_2 100 to 200 mm Hg) of the global epidemiology study LUNG-SAFE.[8] Whilst speculative, if this held true, then the addition of an $ECCO_2R$ machine may add little in terms of benefit, but potentially subject a patient to uncommon, but dangerous, harms from the insertion or presence of the device.

With a predicted mortality of 41%, the trial population was extremely sick, and was ideal to recognise a significant mortality effect if one existed. The inclusion and exclusion criteria were realistic and appropriate. Group allocation was randomised and centrally performed. The open label nature of the trial was unavoidable given the nature of the intervention and it is difficult to ascertain how knowledge of this may have influenced clinicians caring for the intervention group. The trial was largely executed as designed, with high internal validity, which is impressive for a device trial in a very sick population.

The intervention, the combination of an $ECCO_2R$ device with ultra-low tidal volume ventilation, is fascinating to consider. Both components have clinical advantages and disadvantages, the net sum of which is hard to determine unless a robust trial is performed, such as this.

The benefit of the $ECCO_2R$ device is to provide elimination of excessive carbon dioxide load produced by the hypoventilation intrinsic to ultra-low tidal volume ventilation. However, just how much hypercarbia can be tolerated acutely, and the resulting acidaemia, is uncertain, but may be more than was initially thought. The main disadvantage of the $ECCO_2R$ device arises from the systemic anticoagulation necessary to prevent circuit thrombosis. Systemic unfractionated heparin was used, at a dose similar to that for continuous renal replacement therapy. The intervention group had 9 reported episodes of intracranial haemorrhage and 6 episodes of serious bleeding at other sites, as compared to 1 and 0 episodes in the control group, respectively. It may be that the high rates of intracranial haemorrhage seen in REST reflect a vulnerability of a relatively hypoxic brain to intracerebral haemorrhage, which is then exacerbated by systemic anticoagulation. Two single-centre retrospective studies report a prevalence of intracranial haemorrhage of 10.7% and 16.7% when CTs were performed within the first 24 hours of the initiation of ECMO.[9,10] As many ECMO patients are extremely unwell and unable to undergo scanning prior to cannulation and implementation of ECMO, these data may not be easily improved upon.

The perceived benefit of ultra-low tidal volume ventilation was the reduction of ventilator-induced lung injury, and has been addressed above. The potential downside to this strategy was the necessary sedative load required for the patient to tolerate this approach. The trial protocol required $ECCO_2R$ to be used for at least 48 hours. However, patients required significant sedation, and possibly neuromuscular blockade, to tolerate the ultra-low tidal volumes of 3-4 mL/kg. Once a patient entered the trial and was allocated to the intervention arm, they were more deeply sedated, and possibly curarised, for at least 48 hours. While curarisation rates were similar between the groups on day 1, from days 2 to day 7 they were increased in the intervention group (day 2, 25% higher; day 3, 66% higher; and from days 3 to 7, approximately 100% higher). This increase in neuromuscular blockade, and implementation of $ECCO_2R$, was associated with lower tidal volumes (approximately 2-3 mL/kg difference per day) and lower plateau pressures (approximately 2-3 cmH_2O difference per day). In the ACCURSY trial,[11] investigating neuromuscular blockade in ARDS, the implementation of paralysis did not result in differences in tidal volume, plateau pressure or respiratory system compliance on days 1, 3 or 7, suggesting it was the $ECCO_2R$ device which facilitated the observed decrease in ventilation intensity in the intervention group.

Whilst the $ECCO_2R$ machine facilitated the reduction in tidal volume and airway pressures, ironically, it may have caused ventilatory weaning to effectively stop. The intervention could be applied for up to 7 days. The mean duration of $ECCO_2R$ in the trial was 4 days (standard deviation, 2 days). Day 1 was largely consumed with obtaining consent and setting up the $ECCO_2R$ device and transitioning to ultra-low tidal volume ventilation. Between days 2 and 6, PaO_2/FiO_2 was consistently better in the control group and a greater proportion progressed to spontaneous modes of ventilation, equating to between 20% and 25% more per day between days 3 and 7. Once the $ECCO_2R$ machine was withdrawn, a patient in the intervention group was required to wake from the additional sedative load and catch-up the weaning which had occurred in the standard care group. This effective halt on ventilator weaning may have contributed to the two less ventilator-free days in the intervention group.

Despite these selected points being highlighted, ultimately, the trialists designed and executed an excellent trial, which produced high quality data to allow the field to evolve and progress. A clear answer has been delivered from REST – based on the trial as designed and faithfully executed, the combination of ultra-low tidal volume ventilation and $ECCO_2R$ should not be routinely used in patients with acute hypoxaemic respiratory failure. The advances gained from REST are diverse and constructive - patients benefit from the avoidance of this ineffective therapy when used routinely, clinicians benefit from the clarity of effective management options available, researchers benefit from the knowledge gained from REST in designing future studies, and healthcare systems benefit in allocating resources with greater confidence.

Where this sits in the body of evidence

The CESER trial[12] was a UK multicentre randomised controlled trial in 180 patients with potentially reversible severe acute respiratory failure, with a Murray score >3.0 or pH <7.20. 180 patients were randomised to continue receiving conventional management at their current hospital or transfer to a single ECMO centre for ongoing management, including consideration of ECMO. Of the 90 patients managed at the ECMO centre, 68 (75%) actually received ECMO. Survival to 6-months without disability was higher in those managed at the ECMO centre (62%) than those managed conventionally at peripheral centres (47%) (RR, 0.69; 95% CI 0.05 to 0.97, P=0.03). As such this trial compared centres, rather than modality of respiratory support. The trial was criticised for a relatively low rate of protective ventilation at the centres providing conventional treatment.

EOLIA[13] was an international multi-centre trial undertaken in 64 centres in France, the USA, Australia and Canada. 249 patients with severe acute respiratory distress syndrome

(PaO_2/FiO_2 < 50 mm Hg at 3 hours, PaO_2/FiO_2 < 80 mm Hg for > 6 hours, or an arterial blood pH of less than 7.25 with a $PaCO_2$ of at least 60 mm Hg for more than 6 hours) were randomised to either ongoing management with invasive mechanical ventilation or immediate VV-ECMO. 121 of the 124 patients in the ECMO group received this intervention, which was commenced a mean of 3.3±2.8 hours post randomisation. Patients in this group had lower intensity of invasive mechanical ventilation (lower tidal volumes, plateau pressures, driving pressures and respiratory rates). Patients in the control group were managed with protective ventilation, with 90% receiving prone positioning, 83% inhaled nitric oxide and 100% neuromuscular blockade. The 60-day mortality rate was lower in the ECMO group, although it failed to meet statistical significance (35% vs 56%; RR, 0.76; 95% CI, 0.55 to 1.04; P = 0.09).

SUPERNOVA[14] was a French multi-centre phase II trial, investigating the feasibility and safety of ultra-low tidal volume ventilation (4 mL/kg PBW and Pplat ≤ 25 cmH_20) facilitated by $ECCO_2R$ in 95 patients with moderate ARDS (PaO_2/FiO_2 100-200 mm Hg with > 5 cmH_20 PEEP). Three different $ECCO_2R$ devices were used. All patients received sedation and neuromuscular blockade for the first 24 hours. Reduction in ventilatory settings to ultra-low tidal volume ventilation, facilitated by $ECCO_2R$, was performed in three steps. 78% of patients could be managed at these settings at 8 hours and 82% at 24 hours. Two serious adverse events were adjudicated to have been related to $ECCO_2R$. Survival was 62% at hospital discharge and 73% at 28 days.

The Xtravent study[5] was a 10 centre randomised controlled trial undertaken in Austria and Germany between 2007 and 2010. 305 patients were screened and 226 were excluded after improving with a 24 hour period of optimised ventilation. The remaining 79 patients were randomised to either ultra low tidal volume ventilation (≈ 3 mL/kg PBW) facilitated by pumpless arteriovenous (av)$ECCO_2R$ (iLA AV, Novalung, Heilbronn, Germany) or low tidal volume ventilation (≈ 6 mL/kg PBW) in combination with PEEP set by the ARDSnet high PEEP table. Groups were similar at baseline and ultra low tidal volume ventilation was achieved in most patients in the intervention group. Ventilator-free days were similar at day 60 (av$ECCO_2R$ group, 33.2 ± 20 vs control group, 29.2 ± 21; P = 0.469), as was hospital mortality, at 17.5% and 15.4%, respectively. A post hoc analysis identified a higher rate of ventilator-free days at day 60 in the subgroup with severe hypoxaemia (PaO_2/FIO_2 < 150 mm Hg) managed with avECCO2R (40.9 ± 12.8 vs 28.2 ± 16.4; P = 0.033).

In a multi-centre study, Richard and colleagues examined the feasibility of ultra-low tidal volume ventilation without $ECCO_2R$.[7] 35 patients with moderate-to-severe ARDS (PaO_2/FIO_2 < 150 mm Hg) had their tidal volume reduced to 4 mL/kg whilst maintaining a pH > 7.20 by increasing the respiratory rate up to 40 breaths per second. A PEEP-FiO2

table was used to set PEEP. A reduction in tidal volume from 6.0 (5.9 to 6.1) to 4.1 (4.0 to 4.7) mL/kg PBW was associated with a decrease in driving pressure from 12 (9–15) to 8 (6–11) cmH_2O. 65% of patients achieved a tidal volume < 4.2 mL/kg PBW and 88% < 5.25 mL/kg PBW. Ultra low tidal volume ventilation was reasonably well tolerated, with 32% developing a brief severe acidosis (pH < 7.15) and 6% cor pulmonale. Mortality was 41% at 90 days.

Schmidt and colleagues examined the feasibility and safety of a low flow $ECCO_2R$ device as part of a renal replacement therapy platform in 20 patients with mild or moderate ARDS.[15] Tidal volume was incrementally decreased from 6 mL/kg PBW to 4 mL/kg and PEEP was altered to maintain a Pplat between 23 and 25 cm H_20. $ECCO_2R$ was commenced when $PaCO_2$ increased by 20%. With mean $ECCO_2R$ settings of an extracorporeal blood flow of 421 ± 40 ml/min, sweep gas flow of 10 ± 0.3 L/min and arterial CO2 removal of 51 ± 26 ml/min, and without an alteration in respiratory rate, the combination of ultra-low tidal volume ventilation plus $ECCO_2R$ resulted in a $PaCO_2$ increase from 43 ± 8 to 53 ± 9 mm Hg and mean pH decrease of 7.39 ± 0.1 to 7.32 ± 0.10. Mortality was 15% at 28 days.

Should the combination of $ECCO_2R$ and ultra-low tidal volume ventilation be used routinely in patients with acute hypoxaemic respiratory failure?

No. The REST trial provides high quality evidence this approach is currently ineffective

References

1. Montgomery AB, Stager MA, Carrico CJ, Hudson LD. Causes of mortality in patients with adult respiratory distress syndrome. Am Rev Respir Dis 1985;132(3):485–9

2. Stapleton RD, Wang BM, Hudson LD, Rubenfeld GD, Caldwell ES, Steinberg KP. Causes and Timing of Death in Patients With ARDS. Chest 2005;128(2):525–32

3. Goligher EC, Tomlinson G, Hajage D, et al. Extracorporeal Membrane Oxygenation for Severe Acute Respiratory Distress Syndrome and Posterior Probability of Mortality Benefit in a Post Hoc Bayesian Analysis of a Randomized Clinical Trial. JAMA 2018;320(21):2251–9

4. McNamee JJ, Gillies MA, Barrett NA, et al. Effect of Lower Tidal Volume Ventilation Facilitated by Extracorporeal Carbon Dioxide Removal vs Standard Care Ventilation

on 90-Day Mortality in Patients With Acute Hypoxemic Respiratory Failure: The REST Randomized Clinical Trial. JAMA 2021;326(11):1013–23

5. Bein T, Weber-Carstens S, Goldmann A, et al. Lower tidal volume strategy (≈ 3 ml/kg) combined with extracorporeal CO 2 removal versus 'conventional'protective ventilation (6 ml/kg) in severe ARDS. Intensive Care Med 2013;39(5):847–56

6. Amado-Rodríguez L, Del Busto C, López-Alonso I, et al. Biotrauma during ultra-low tidal volume ventilation and venoarterial extracorporeal membrane oxygenation in cardiogenic shock: a randomized crossover clinical trial. Ann Intensive Care 2021;11(1):1–10

7. Richard JC, Marque S, Gros A, et al. Feasibility and safety of ultra-low tidal volume ventilation without extracorporeal circulation in moderately severe and severe ARDS patients. Intensive Care Med 2019;45(11):1590–8

8. Bellani G, Laffey JG, Pham T, et al. Epidemiology, patterns of care, and mortality for patients with acute respiratory distress syndrome in intensive care units in 50 countries. JAMA 2016;315(8):788–800

9. Arachchillage DR, Passariello M, Laffan M, et al. Intracranial hemorrhage and early mortality in patients receiving extracorporeal membrane oxygenation for severe respiratory failure. Semin Thromb Hemost 2018;44(03):276–86

10. Lockie CJ, Gillon SA, Barrett NA, et al. Severe respiratory failure, extracorporeal membrane oxygenation, and intracranial hemorrhage. Crit Care Med 2017;45(10):1642–9

11. Papazian L, Forel J-M, Gacouin A, et al. Neuromuscular Blockers in Early Acute Respiratory Distress Syndrome. N Engl J Med 2010;363(12):1107–16

12. Peek GJ, Mugford M, Tiruvoipati R, et al. Efficacy and economic assessment of conventional ventilatory support versus extracorporeal membrane oxygenation for severe adult respiratory failure (CESAR): a multicentre randomised controlled trial. Lancet 2009;374(9698):1351–63

13. Combes A, Hajage D, Capellier G, et al. Extracorporeal membrane oxygenation for severe acute respiratory distress syndrome. N Engl J Med 2018;378(21):1965–75

14. Combes A, Fanelli V, Pham T, Ranieri VM. Feasibility and safety of extracorporeal CO 2 removal to enhance protective ventilation in acute respiratory distress syndrome: the SUPERNOVA study. Intensive Care Med 2019;45(5):592–600

15. Schmidt M, Jaber S, Zogheib E, Godet T, Capellier G, Combes A. Feasibility and safety of low-flow extracorporeal CO 2 removal managed with a renal replacement platform to enhance lung-protective ventilation of patients with mild-to-moderate ARDS. Crit Care 2018;22(1):1–8

HOT-ICU

Schjørring OL, Klitgaard TL, Perner A, Wetterslev J, Lange T, Siegemund M, et al. Lower or Higher Oxygenation Targets for Acute Hypoxemic Respiratory Failure. N Engl J Med 2021; 384:1301-1311

Introduction

Respiratory failure is one of the commonest reasons for admission to the ICU. In 2017 in the USA, there were an estimated 1,146,195 episodes of mechanical ventilation for this reason.[1] Oxygen therapy is a cornerstone of management of patients with acute respiratory failure, with clinicians having to actively choose a fraction of inspired oxygen to deliver to their patients in response to their physiological state. However, this choice of which target oxygenation range to opt for is unclear. While supplemental oxygen is lifesaving in the setting of hypoxaemia, enabling ongoing generation of energy via the oxidative phosphorylation chain in mitochondria, it is also highly reactive, requiring a complex system of endogenous antioxidants to limit oxidative damage to tissues.

Hyperoxaemia is injurious to the lung, including tracheitis, bronchitis, alveolitis, interstitial fibrosis and atelectasis, as well as doubling the risk of ICU-acquired weakness.[2] In addition, it can produce vasoconstriction in the heart and brain, as well as systemically, and paradoxically can induce tissue ischaemia.[3] Accumulating evidence from trials in the setting of myocardial infarction,[4] cardiac arrest,[5] stroke[6] and sepsis[2] suggest hyperoxaemia may be harmful. However, while there is an association between hyperoxaemia and worse outcomes, it is unclear if targeting a lower oxygenation range might be a better option. Although a value as low as 24.6 mm Hg (3.28 kPa) has been recorded in healthy mountaineers breathing ambient air at 8400 metres on top of Mount Everest, it is very unlikely this is generalisable to elderly, multi-morbid, acutely ill patients with organ failure. A number of trials[7–11] comparing high and lower oxygenation ranges in the critically ill have been performed to date, with meta analysis[3] suggesting a possible improvement in mortality with a conservative oxygenation strategy in patients with mild-to-moderate hypoxemia.

Synopsis

The Handling Oxygenation Targets in the ICU (HOT-ICU) trial was an investigator-initiated, international, multi-centre, stratified, parallel group, open-label, randomised controlled trial. It was conducted 35 ICUs in 7 European countries between 2017 and 2020. The results were reported at the eCCR21 virtual conference on January 20th, 2021, and simultaneously published in the *New England Journal of Medicine*.

Eligible patients were adults being treated in the ICU with acute respiratory failure and requiring oxygen at either greater than 10 l/min in an open delivery system or with a fraction of inspired oxygen (FiO_2) > 0.5 in a closed system. Supplemental oxygen was expected to be delivered for at least a further 24 hours and an arterial line, to facilitate blood gas monitoring, was required. Exclusion criteria specific to this trial included an ICU admission lasting > 12 hours, being in receipt of chronic mechanical ventilation or domiciliary oxygen, previous bleomycin therapy, organ transplantation, or a condition with a requirement for a higher oxygen target, including carbon monoxide poisoning, cyanide poisoning, paraquat poisoning, methaemoglobinaemia, or sickle cell disease.

Patients were randomly allocated in a 1:1 fashion to either a lower- or higher- oxygen target group. Randomisation was achieved in a blinded fashion, via a centralised web-based system using permuted blocks of varying sizes. This was stratified by site and the presence of chronic obstructive pulmonary disease or active haematological malignancy.

Patients randomised to the lower oxygenation group had a target PaO_2 of 60 mm Hg (8.0 kPa) and those randomised to the higher oxygenation group had a target PaO_2 of 90 mm Hg (12.0 kPa). The trial period lasted 90 days from randomisation. Oxygen targets ceased on transfer to general wards, but were recommenced during any periods of readmission to the ICU. There was no specific oxygenation measurement protocol, but it was expected a minimum of 4 arterial blood gas measurements would occur per 24 hour period. Between these periods of arterial blood gas measurement, peripheral oxygen saturation was used to guide therapy, with staff instructed to maintain the SpO_2 at which the assigned PaO_2 was obtained. Changes in oxygenation were achieved by altering the FiO_2. Patients had their invasive ventilation, non-invasive ventilation, or continuous positive airway pressure settings reviewed and adjusted at 8am daily.

The primary outcome measure was mortality at day 90. Based on an expected 90-day mortality of 25% in the higher oxygenation group, 2928 patients were required to identify a 5% absolute mortality reduction in the lower oxygenation group, with 90% power at a two-sided alpha level of 5%. Three secondary outcomes were tested: the number of patients with ≥ 1 serious adverse event, the percentage of days alive without life support, and the percentage of days patients alive after hospital discharge at day 90. Analysis of these secondary outcomes was corrected for multiple testing and required a P value < 0.0125 to achieve statistical significance. An intention-to-treat design was used. A planned interim analysis occurred after day 90 data was available for 1464 patients.

4192 patients were screened and 1264 patients were excluded, mainly for an inability to randomise within 12 hours of ICU admission, a lack of consent, domiciliary oxygen use, or

imminent death. 1462 patients were randomised to the lower oxygenation group and 1466 to the higher oxygenation group. 40 patients were excluded, mostly due to withdrawal or unobtainable consent, leaving 1441 and 1447 patients for analysis in the two groups, respectively.

Groups were similar at baseline. The median patient age was 70 years and 64% were male. Patients had been in hospital for a median of 1 day prior to randomisation and had an interval of 4 hours from ICU admission to randomisation. 14% had ischaemic heart disease and 19% chronic obstructive pulmonary disease. Most patients had a medical cause of their acute illness (85%), with pneumonia being the most common condition (57%). 57.4% and 59.7% of patients in the lower and higher oxygenation groups were receiving invasive mechanical ventilation at the time of entry into the trial, respectively; 13% of both groups had acute respiratory distress syndrome. The median PaO_2 at baseline was similar in both groups at 77.3 mm Hg (SpO_2 94-95%). The median PaO_2/FiO_2 was approximately 118 mm Hg. Groups had similar severity of illness measures; median SOFA 9 vs 9, and median lactate level 1.8 vs 1.7 mmol/L, respectively.

Good separation in oxygenation was achieved between the two groups. The higher oxygenation group had a median higher daily mean PaO_2 (93.3; IQR 87.1 to 98.7 mm Hg) than the lower group (70.8; IQR 66.6 to 76.5 mm Hg). Peripheral oxygenation saturations were consistent with the partial pressure measurements (96% vs 93%). This difference in oxygenation corresponded to a divergence in median delivered FiO_2 between the higher oxygenation group (0.56; IQR, 0.46 to 0.71) and the lower oxygenation group (0.43; IQR, 0.34 to 0.54). A similar proportion of both groups received invasive mechanical ventilation (low vs high groups; 68.4% vs 71.2%), which was delivered with comparable effects: tidal volume, 7.3 vs 7.3 ml/kg predicted body weight; peak pressure, 22 vs 22 cmH_20; PEEP, 9 vs 8 cmH_20. Additional respiratory interventions which could bias these results were used with similar frequencies in the two group: prone positioning (low vs high groups; 4.9% vs 6.6%), inhaled pulmonary vasodilators (3.4% vs 5.1%), and extracorporeal membrane oxygenation (ECMO) (0.9% vs 0.9%).

The primary outcome of mortality at day 90 occurred in 42.9% of the lower oxygenation group and 42.4% of the higher group, a difference that was not statistically significant (RR, 1.02; 95% CI, 0.94 to 1.11; P = 0.64). Secondary outcomes were coherent with the primary outcome, with no significant difference in median percentage of days alive without life support (87.8% vs 84.4%; P=1.0), median percentage of days alive after hospital discharge (55.6 vs 50.0; P=0.67) and serious adverse events (36.1% vs 38.1%; RR, 0.95; 95% CI, 0.84 to 1.07; P=0.24). There was little difference in the incidences of the various measured adverse events; shock (34 vs 36%), myocardial ischaemia (1.0 vs 0.5%),

ischaemic stroke (1.3% vs 1.6%) and intestinal ischaemia (2.2 vs 2.0%). Sensitivity and subgroup analyses were consistent with the primary and secondary outcomes.

Critique

HOT-ICU is an excellent example of a modern critical care trial – international, robust, internally and externally valid, and designed and executed by a highly experienced core set of trialists. As such, it is an excellent addition to the evidence base. It is increasingly becoming clear, that for most patients in the ICU, the choice of either a higher or lower oxygenation target, whilst avoiding hyperoxaemia or severe hypoxaemia, will probably have little effect on mortality. However, given that up to 20 million people may receive invasive mechanical ventilation in the ICU per year, even a small effect may result in a significant number of lives saved. Equally, larger subgroups may provide additional information about important populations, such as those at risk for hypoxaemic-ischaemic encephalopathy post cardiac arrest. The visionary MEGA-ROX trial (ACTRN12620000391976), aiming to recruit 40,000 patients, will further inform this field in due course.

An unavoidable limitation of the trial was its open-label nature. Clinicians require accurate knowledge of the oxygenation status of their patients to guide management, so blinding to this variable was not feasible. There was no evidence from the presented data that either a lower or higher oxygenation target influenced practice, with both groups having similar ventilatory settings, as well as comparable use of rescue therapies, such as prone positioning, inhaled pulmonary vasodilators and ECMO. Use of non-pulmonary organ support was also similar between the two groups.

Although there was no discernible signal of either benefit or harm from the alternative oxygenation targets in this robust trial, there is little to suggest this is a false negative finding. The unexpectedly high mortality rate, twice that originally anticipated, should have enriched the trial population, making them more susceptible to benefit from a reduced potential inflammatory injury from the lower oxygen target. This implies any potential pathophysiological modulation was minor and insufficient to alter outcomes.

With almost identical outcomes occurring between the two target oxygenation ranges (8 kPa and 12 kPa / 60 and 90 mm Hg), a logical next step is to consider just how low oxygenation targets could be tolerated in critically ill patients, often elderly with chronic cardiovascular disease. Despite being far removed from the typical elderly co-morbid adult ICU patient, there are intriguing paediatric data to consider. Firstly, the BOOST II trial compared oxygen saturation targets of 85 to 89% with 91 to 95% in 2108 infants in Australia & the UK born before 28 weeks gestation. In a combined analysis including all patients, the infants managed with the lower SpO_2 target range had an increased rate of

both death and disability (48.1% versus 43.1%; RR, 1.11; 95% CI, 1.01 to 1.23; P=0.02), and death (21.2% versus 17.7%; RR, 1.20; 95% CI, 1.01 to 1.43; P=0.04).[12] Clearly, a preterm infant population is unique, both in terms of the pathologies being managed and typical competing complications, such as necrotizing enterocolitis and retinopathy of prematurity. Oxygenation strategies in a slightly older population of African children with severe pneumonia have also been investigated.[13] In a group of 727 infants with peripheral oxygen saturations between 80% and 90%, and being managed with permissive hypoxaemia, just 15% required supplement oxygen for a decrease in SpO_2 to < 80%. The 48 hour mortality in this permissive hypoxaemia group was 1.4%, in comparison with a combined group, receiving either high flow nasal therapy (n=363) or low flow oxygen therapy (n=364), of 1.7%. The adjusted odds ratio for death at 48 hours in the combined group relative to the permissive hypoxaemia group was 1.16 (95% CI, 0.49 to 2.74; P = 0.728).

The longer term effects of different oxygenation strategies are equally important to consider. The Adult Respiratory Distress Syndrome Cognitive Outcomes Study,[14] which reported the 1 year outcomes of ARDSnet Fluid and Catheter Treatment Trial,[15,16] described an association between a lower PaO_2 and both cognitive and psychiatric impairment in 261 survivors. Recently, the longer term outcomes of the HOT-ICU trial have also been reported.[17] One year mortality was remarkably similar between the two groups (49% vs 48.7%, in the lower and higher target groups, respectively). Typical of survivors of acute respiratory failure and ARDS,[18] the entire cohort had impairments in all 5 domains of the EuroQol five dimensions five level (mobility, self-care, usual activities, pain or discomfort, and anxiety or depression), which were most marked in the mobility, usual activities and pain/discomfort dimensions. There were no discernible differences in outcomes between the two oxygenation strategies.

Where this sits in the body of evidence

CLOSE[10] was an unblinded, pilot, parallel group, randomised controlled trial evaluating the feasibility of comparing a restrictive oxygenation strategy with a liberal oxygenation strategy in patients receiving invasive mechanical ventilation in the ICU for less than 24 hours and expecting to continue receiving this for an additional 24 hours. The restrictive group had a target SpO_2 of 88-92% and the liberal group a target $SpO_2 \geq 96\%$. The trial ran in 4 centres in 3 countries between 2013 and 2014. 52 patients were randomised to the restrictive oxygen group and 51 to the liberal oxygen group. The oxygenation targets for each group were achieved (mean SpO_2 93% vs 97%), confirming the feasibility of a larger trial. Oxygenation values were off target just 6% of the total time. There was no signal of harm with a restrictive approach. SpO_2 was < 88% just 1% of the time in the restrictive group and was > 98% 22% of the time in the liberal group. 90 day mortality was 40% and 37% in the restrictive and liberal groups, respectively (P=0.74).

OXYGEN-ICU[7] was an Italian, single centre, open-label, parallel group, randomised controlled trial comparing conservative and liberal oxygen therapy in patients expected to remain in the ICU for at least 72 hours. The conservative arm had their PaO_2 maintained between 70 and 100 mm Hg (SpO_2 94% to 98%) and the liberal group had theirs maintained up 150 mm Hg (SpO_2 97% to 100%). The trial was stopped early after an unplanned analysis, due to difficulties in recruitment, partly from the effects from an earthquake in the region and partly due to an anticipated loss of equipoise amongst nursing staff. 480 out of a planned 660 patients had been recruited. 434 patients were included in the modified intention-to-treat analysis. The conventional group had a higher daily time-weighted FiO_2 (median FiO_2, 0.39 vs 0.36) and median PaO_2, (102 mm Hg vs 87 mm Hg; P < 0.001). ICU mortality was lower in the conservative group; 11.6% vs 20.2% (difference, 8.6%; 95% CI, 1.7% to 15.0%; P=0.01). Hospital mortality was also lower in the conservative group (24% vs 33.9%; P=0.03), as was the proportion with liver failure (1.9% vs 6.4%, P=0.02), new episodes of bacteraemia (5.1 vs 10.1%; P=0.049) and mechanical ventilation free hours (72 vs 48; P=0.02).

ICU-ROX[9] was a 1000 patient pilot trial comparing a conservative oxygenation strategy, aimed at reducing oxygen exposure, with standard care. It took place in 21 ICUs in Australia and New Zealand between 2015 and 2018. Patients in the conservative arm were managed between SpO_2 values of 90% and 97%. The standard care arm had a lower SpO_2 limit of 90% and no upper limit. All adult patients being treated in the ICU with an expected length of stay until at least two days. The primary outcome was the number of ventilator-free days at day-28, and was similar in both groups; median duration 21.3 days vs 22.1 days in the conservative and liberal groups, respectively (difference -0.3 days; 95% CI, -2.1 to 1.6; P=0.80). Mortality at 180 days was also similar between the two groups, 35.7% vs 34.5%, respectively.

LOCO2[8] was a French multi-centre, open-label, randomised controlled trial which compared higher (PaO_2 target 90 to 105 mm Hg) and lower (PaO_2 target 55 to 70 mm Hg) oxygenation targets in patients with ARDS receiving invasive mechanical ventilation. 850 patients were required at identify a 9% reduction in 28 day mortality with the conservative oxygenation strategy, from a baseline of 30% in the liberal group to 21% in the conservative group. Both groups were managed with the same ventilatory protocol. The trial was stopped early, with 205 patients enrolled, after an interim analysis identified a low likelihood of achieving a significant difference in the primary outcome of mortality at day 28, and a signal of harm in the lower oxygenation group, due to an excess of cases of mesenteric ischaemia (5 vs 0). The primary outcome occurred in 34.3% of the lower oxygenation group and 26.5% of the higher oxygenation

group, a difference of 7.8% (95% CI, −4.8 to 20.6). Mortality at day 90 was 44.4% in the conservative group and 30.4% in the liberal group (difference, 14%; 95% CI, 0.7 to 27.2)

O2-ICU[11] was a randomised controlled trial undertaken in 4 Dutch ICUs between 2015 and 2018. It compared a lower PaO_2 target of 8 to 12 kPa (n = 205) and a higher PaO_2 target of 14 to 18 kPa (n = 195). Eligible patients had been admitted to the ICU with 2 or more systemic inflammatory response syndrome criteria and had an expected stay of longer than 48 hours. All modes of supplemental oxygen were eligible for inclusion. The median difference in PaO_2 between the groups was 1.93 kPa (95% CI, −2.12 to −1.74; P < 0.001). The primary outcome was the $SOFA_{RANK}$ over the first 14 days, a measure of organ dysfunction, with lower scores indicating less organ failure severity. The median $SOFA_{RANK}$ score decreased by 35 points in the lower PaO_2 group and by 40 points in the higher PaO_2, a difference which was not statistically significant (median difference, 10 points; 95% CI, 0 to 21; P = 0.06). There were no significant differences in secondary endpoints, including median duration of mechanical ventilation (3.4 vs 3.1 days; difference, −0.15; 95% CI, −0.88 to 0.47; P = 0.59) and in-hospital mortality (32% vs 31%; OR, 1.04; 95% CI, 0.67 to 1.63; P = 0.91).

COAST[13] was an open-label fractional-factorial randomised controlled trial investigating oxygenation targets in African children with severe pneumonia. Depending on the baseline SpO_2, patients were enrolled into two strata, a hypoxaemic stratum (SpO_2 80 to 91%) and a severe hypoxaemic stratum (SpO_2 < 80%). In the hypoxaemic stratum, patients were randomised in a 1:1:2 fashion to either high flow nasal therapy (using either air or blended oxygen depending on the SpO_2; n=363), low flow oxygen (face mask or nasal cannulae; n=364) or permissive hypoxaemia (n=727). Patients in the severe hypoxaemic stratum were randomised to high flow nasal therapy (air or blended oxygen; n=194) or low flow oxygen (n=194). The target SpO_2 was ≥ 92% breathing room air. Patients in the permissive hypoxaemia group received low flow oxygen if their SpO_2 fell below 80%. The trial was stopped early after recruiting 1852 out of a planned 4200 children, due to recruitment difficulties. Adherence to the protocol was excellent and the primary outcome was recorded for almost all patients. Just 15% of the permissive hypoxaemia group required oxygen therapy. In the severe hypoxaemia stratum, the primary endpoint of mortality at 48 hours occurred in 9.3% receiving HFNT and 13.4% in the low flow oxygen group. In the hypoxaemic stratum, 48 hour mortality was 1.1% in the high flow group, 2.5% in the low flow oxygen, and 1.4% in the permissive hypoxaemia group. The primary analysis compared firstly, high flow therapy with low flow oxygen, and secondly, liberal therapy (high flow or low flow) with permissive hypoxaemia. The adjusted odds ratio for high flow therapy versus low flow oxygen was 0.60 (95% CI, 0.33 to 1.06; P=0.076) and for liberal therapy versus permissive hypoxaemia was 1.16 (95% CI, 0.49 to 2.74; P= 0.728).

Should we use higher or lower oxygenation targets in critically ill patients?

At present, it appears there is little difference in outcomes between patients managed with either liberal or conservative oxygenation targets in the ICU.

References

1. Kempker JA, Abril MK, Chen Y, Kramer MR, Waller LA, Martin GS. The Epidemiology of Respiratory Failure in the United States 2002–2017: A Serial Cross-Sectional Study. Crit Care Explor 2020;2(6):e0128.

2. Asfar P, Schortgen F, Boisramé-Helms J, et al. Hyperoxia and hypertonic saline in patients with septic shock (HYPERS2S): a two-by-two factorial, multicentre, randomised, clinical trial. Lancet Respir Med 2017;5(3):180–90.

3. Chen X-L, Zhang B-L, Meng C, Huang H-B, Du B. Conservative oxygen therapy for critically ill patients: a meta-analysis of randomized controlled trials. J Intensive Care 2021;9(1):47.

4. Stub D, Smith K, Bernard S, et al. Air Versus Oxygen in ST-Segment–Elevation Myocardial Infarction. Circulation 2015;131(24):2143–50.

5. Kilgannon JH, Jones AE, Shapiro NI, et al. Association Between Arterial Hyperoxia Following Resuscitation From Cardiac Arrest and In-Hospital Mortality. JAMA 2010;303(21):2165–71.

6. Rincon F, Kang J, Maltenfort M, et al. Association between hyperoxia and mortality after stroke: a multicenter cohort study. Crit Care Med 2014;42(2):387–96.

7. Girardis M, Busani S, Damiani E, et al. Effect of conservative vs conventional oxygen therapy on mortality among patients in an intensive care unit: the oxygen-ICU randomized clinical trial. JAMA 2016;316(15):1583–9.

8. Barrot L, Asfar P, Mauny F, et al. Liberal or conservative oxygen therapy for acute respiratory distress syndrome. N Engl J Med 2020;382(11):999–1008.

9. Mackle D, Bellomo R, Bailey M, et al. Conservative Oxygen Therapy during Mechanical Ventilation in the ICU. N Engl J Med 2020;382(11):989–98.

10. Panwar R, Hardie M, Bellomo R, et al. Conservative versus liberal oxygenation targets for mechanically ventilated patients. A pilot multicenter randomized controlled trial. Am J Respir Crit Care Med 2016;193(1):43–51.

11. Gelissen H, de Grooth H-J, Smulders Y, et al. Effect of low-normal vs high-normal oxygenation targets on organ dysfunction in critically ill patients: a randomized clinical trial. JAMA 2021;326(10):940–8.

12. BOOST-II Australia and United Kingdom Collaborative Groups, Tarnow-Mordi W, Stenson B, et al. Outcomes of Two Trials of Oxygen-Saturation Targets in Preterm Infants. N Engl J Med 2016;374(8):749–60.

13. Maitland K, Kiguli S, Olupot-Olupot P, et al. Randomised controlled trial of oxygen therapy and high-flow nasal therapy in African children with pneumonia. Intensive Care Med 2021;47(5):566–76.

14. Mikkelsen ME, Christie JD, Lanken PN, et al. The Adult Respiratory Distress Syndrome Cognitive Outcomes Study. Am J Respir Crit Care Med 2012;185(12):1307–15.

15. The National Heart, Lung, and Blood Institute Acute Respiratory Distress Syndrome (ARDS) Clinical Trials Network. Pulmonary-Artery versus Central Venous Catheter to Guide Treatment of Acute Lung Injury. N Engl J Med 2006;354(21):2213–24.

16. National Heart, Lung, and Blood Institute Acute Respiratory Distress, Syndrome (ARDS) Clinical Trials Network. Comparison of Two Fluid-Management Strategies in Acute Lung Injury. N Engl J Med 2006;354(24):2564–75.

17. Crescioli E, Klitgaard TL, Poulsen LM, et al. Long-term mortality and health-related quality of life of lower versus higher oxygenation targets in ICU patients with severe hypoxaemia. Intensive Care Med 2022;1–9.

18. Herridge MS, Tansey CM, Matté A, et al. Functional Disability 5 Years after Acute Respiratory Distress Syndrome. N Engl J Med 2011;364(14):1293–304.

COAST

Maitland K, Kiguli S, Olupot-Olupot P, Hamaluba M, Thomas K, Alaroker F, et al. Randomised controlled trial of oxygen therapy and high-flow nasal therapy in African children with pneumonia. Intensive Care Medicine 2021;47:566–576

Introduction

Oxygen is the Earth's most abundant element and is the third most abundant in the universe.[1] It is intrinsically linked with life on Earth. 2.8 billion years ago cyanobacteria began to generate oxygen by photosynthesis, causing a ten-fold rise in its atmospheric concentration to 21%.[2] This change, termed the Great Oxygenation Event, was dramatic, and facilitated the evolution of aerobic respiration, a far more powerful mode of metabolism than anaerobic respiration.

The use of oxygen is ubiquitous in medicine, especially in critical care. It was first identified by Michael Sendivogius in 1604, but its discovery was popularly attributed to Joseph Priestley, in 1774, although Carl Wilhelm Scheele may have preceded him in 1773. Antoine Lavoisier initially used the term oxygen 1777.[1] One of the earliest recorded therapeutic uses of oxygen was by the French physician Caillens in 1783, prescribing daily inhalations for a young woman with tuberculosis.[3] Throughout the 1800s, oxygen was touted as a remedy for many ailments, including in the form of oxygenated water and bread! Although many of these "treatments" were derided. In 1890 Dr Albert Blodgett used oxygen to treat a woman with pneumonia in respiratory distress.[3] This was published in the *Boston Medical and Surgical Journal,* the antecedent of the *New England Journal of Medicine.*[4]

Despite being used for over a century and a quarter, oxygen has never been subjected to a randomised controlled trial evaluating its efficacy in acute respiratory failure. Given the scarcity of availability in less well resourced settings, the efficacy and thresholds of its administration are long overdue.

Synopsis

The Children's Oxygen Administration Strategies Trial (COAST) was a binational, multi-centre, open-label, stratified, fractional-factorial randomised controlled trial. It was conducted in four Ugandan and two Kenyan hospitals between 2017 and 2020 and was published in Intensive Care Medicine in May, 2021.

Two hypotheses were tested in COAST; firstly, would a liberal oxygenation strategy, compared with permissive moderate hypoxaemia, decrease mortality in hypoxaemic

African children with pneumonia and peripheral oxygenation strategies between 80% and 91%; and secondly, whether high-flow nasal therapy would decrease mortality compared with low-flow oxygen therapy, again in hypoxaemic African children with severe pneumonia

Eligible patients were children aged between 28 days and 12 years, with suspected pneumonia and hypoxaemia, defined as a peripheral pulse oximetry reading < 92% whilst breathing room air for > 5 minutes. Exclusion criteria were uncorrected cyanotic heart disease, previous oxygen therapy for this illness provided elsewhere, known chronic lung disease, and prior enrolment.

Randomisation was with consecutively number packs containing randomised links to opaque sealed envelopes and was similar to the process previously used in the FEAST and TRACT trials. Participants were allocated on a 2:1 basis to two strata depending on SpO_2; a hypoxaemic stratum (SpO_2 80% to 91%) and a severely hypoxaemic stratum (SpO_2 <80%). Co-enrolment in other trials was not permitted. In the hypoxic stratum (SpO_2 80% to 91%), participants were randomly allocated in a 1:1:2 fashion to either high flow nasal therapy, low flow nasal therapy, or permissive hypoxaemia. The aim of treatment with high flow nasal therapy and low flow oxygen was to maintain a SpO_2 > 92%. The high flow nasal therapy could be with either air or air or blended with oxygen, as required to maintain oxygenation. The device, AIRVO™2 (Fisher and Paykel Healthcare) provided a warmed, humidified flow of air or oxygen-enriched air. A protocol dictated how flow rates and FiO_2 should be managed. Low flow oxygen was delivered via either nasal cannulae, or face mask should a higher flow rate be needed. Children receiving high-flow or low-flow had a target SpO_2 > 92%. Therapy could be weaned and stopped after two hours of adequate oxygenation provided the SpO_2 was maintained. Permissive hypoxia was tolerated unless the SpO_2 fell < 80%, at which point low flow oxygen was introduced. For the second stratum of severe hypoxaemia, participants were randomised to either high-flow nasal therapy or low flow oxygen therapy only.

Participants were cared for on general paediatric wards. All other interventions were at the discretion of the treating clinicians and followed standard practice and international guidelines.

The primary outcome was mortality at 48 hours. The sample size was generated with simulations based on data from the FEAST trial and Kilifi Hospital in Kenya. Premised on 48 hour mortality rates of 9% in patients with oxygen saturations of 80% to 91% treated with low flow oxygen, and 26% in those with SpO_2 < 80% also treated low flow oxygen, 4200 patients were required to identify, with 90% power, a 33% relative risk reduction with liberal therapy in the hypoxaemic stratum, and a 25% relative risk reduction with

high-flow nasal therapy in the severe hypoxaemia stratum. Three interim analyses were planned with early stopping rules incorporated for either harm or benefit. Analyses were undertaken on an intention-to-treat principle.
The trial was stopped early for feasibility due to opponents in Uganda claiming the trial was unethical. Recruitment in this country had already been halted several times due to a civil society group claiming it deprived children of oxygen which was recommended in guidelines. After several hiatuses, impeding enrolment for 15 of the 35 months COAST had been open, the trial steering committee recommended to the sponsor that the trial was no longer feasible.

1842 children had been enroled to this point, 1454 to the hypoxaemic stratum (high flow, n=363; low-flow, n=364; permissive hypoxaemia, n=727) and 388 to the severely hypoxaemic stratum (high flow, n=194; low-flow, n=194). Three patients absconded and 1 withdrew. At baseline, in the hypoxaemia stratum, the median age was approximately 9.5 months, 59% were male, the median SpO_2 was 88%, median weight 8.1 kg and 40% were in compensated shock. Approximately 6% had confirmed malaria. In the severe hypoxaemia stratum, the median age was approximately 7 months, 49% were male, the median SpO_2 was 75%, median weight 6.7 kg and 61% were in compensated shock. Approximately 6.5% had confirmed malaria.

	Severe Hypoxaemia		***Hypoxaemia***		
	High-Flow	***Low-Flow***	***High-Flow***	***Low-Flow***	***Permissive Hypoxaemia***
48 hour mortality	9.3%	13.4%	1.1%	2.5%	1.4%
48 hour treatment failure	8.6%	10.8%	1.4%	2.3%	4.6%
28 day mortality	18.6%	23.4%	3.3%	4.1%	3.9%
28 day neurocognitive sequelae	3.8%	5.4%	2.6%	3.2%	2.3%

Table 5. Primary outcome at 48 hours and secondary outcomes
Data was available for 1838 out of 1424 enrolled patients

Adherence with the protocol was excellent, with just 6 out of 1842 children not starting their assigned treatment, 3 of whom died rapidly, prior to commencing therapy. Just 5 protocol deviations were recorded. There was a clear difference in oxygen usage in the hypoxaemia stratum, with the mean number of litres of oxygen used being 969 in those receiving high-flow nasal therapy, 1481 in those receiving low-flow nasal therapy and 359 in those assigned to permissive hypoxaemia. In the other stratum, again those

assigned to high-flow nasal therapy used less oxygen than those receiving low-flow oxygen (2731 versus 3591 L). In the hypoxaemia stratum, less patients required a dose escalation in the permissive hypoxaemia group (15%) than the low-flow group (48.9%) or the high-flow group (60.2%). In the severe hypoxaemia stratum, these values were less divergent, being 85.1% in the low-flow group and 89.7% in the high-flow group.

In the a priori analysis comparing liberal therapy (high-flow plus low-flow groups) with permissive hypoxaemia, there was no significant difference in the adjusted odds ratio for the primary outcome (1.16; 95% CI 0.49, 2.74; P = 0.728). In the severe hypoxaemia group, there was again no statistically significant difference between the two interventions (aOR, 0.60; 95% CI, 0.33 to 1.06; P= 0.076) for the primary outcome. The secondary outcomes, including 28 day mortality and neurocognitive sequelae at 28 days, were coherent with the primary outcome in both strata. Treatment failure at 48 hours occurred less often in the liberal group than the permissive hypoxaemia group (aOR, 0.37; 95% CI, 0.19 to 0.71), and in the high-flow group than the low flow-group (aOR 0.75; 95% CI, 0.40 to 1.41). Length of hospital stay and readmission rates were similar between groups.

Critique

COAST was another outstanding trial from the Kilifi Clinical Trials Facility, supported by the Wellcome Trust, and follows the landmark FEAST[5] and TRACT[6,7] projects. Although oxygen is a cornerstone of acute medicine, the parameters of its use have only recently begun to be investigated. While the potential harms of hyperoxia have been investigated in various conditions, including stroke, myocardial infarction and cardiac arrest, and relative limits of hypoxia have been examined in the ICU setting, no trial has yet formally compared oxygen with no oxygen in the setting of hypoxaemic respiratory failure. As such, this is another first from a group that has long challenged medical orthodoxy and promoted scientific standards for interventions in acute care.

The design and execution of COAST in a resource-limited setting was superb. Extensive training and education was provided to the centres, with resultant excellent protocol compliance. Patients were recruited early after presentation to healthcare facilities, optimising the chances for a potential effect to be identified. Excellent separation was achieved in terms of exposure to supplemental oxygen and oxygen saturations. Participant follow up was remarkable within this environment, with just 4 out of 1,842 patients missing data for their primary outcome, 3 of whom absconded. At 28 days, at which point the vast majority of patients had returned home, data was missing for just 16 patients.

While the internal validity of the trial appears high, the external validity is less clear. With 1842 children recruited across two African countries, COAST is highly probable to be generalisable to similar healthcare systems. It is less clear how this relates to more advanced healthcare systems, and indeed to adults, given the median age of participants was just 9.5 months. While paediatric physiology will be unchanged across different regions, pathologies may change, as may nursing ratios, monitoring, and available interventions. Hopefully, there won't be a decade long delay before this trial is replicated, as has happened with FEAST.

Another aspect of the generalisability of COAST is the choice of intervention for children with pneumonia and hypoxaemia. The recently reported FIRST-ABC trial (Step-Up arm)[8] compared high flow nasal cannulae (HFNC) with continuous positive airway pressure (CPAP) in 600 children with acute respiratory failure post extubation. It found HFNC not to be non-inferior to CPAP, with respect to the primary intervention of time to liberation from respiratory support (50.5 hours vs 42.9 hours, respectively). At 180 days, mortality was significantly higher for those treated with HFNC (5.6% vs 2.4%; aOR, 3.07; 95% CI, 1.1 – 8.8]. The results of the Step-Up arm, comparing HFNC with CPAP in children with a requirement non-invasive ventilation, will be presented at the Critical Care Reviews Meeting 2022. With a highly exaggerated extrapolation, could it be that the choice of intervention becomes either no oxygen or CPAP?

The sample size was calculated on an estimated 48 hour mortality of 26% in the severe hypoxaemia stratum and 9% in the hypoxaemia stratum. The actual mortality in the two treatment arms of the severe hypoxaemia stratum was 9.3% and 13.4%, and in the hypoxaemia stratum was between 1.1 and 2.5%. This loss of power was likely important and nuances the interpretation of the 48 hour mortality rates. Although no statistically significant results were found, a clear numerical difference was seen which requires further research to confirm or repudiate.

Unfortunately, the trial was hampered by opposition within Uganda, claiming the trial was unethical, despite support for it by the Ugandan Paediatric Association. The trial was stopped three times and restarted twice, before becoming unfeasible within the remaining funding timeframe.[9] With the tantalising results obtained on just 44% of the intended sample size, COAST leaves the question as to just what degree of hypoxia can be safely tolerated very much alive.

Where this sits in the body of evidence

The PARIS trial[10] was a randomised controlled trial undertaken in 17 hospitals in Australia and New Zealand between 2013 and 2016. It compared the use of high-flow nasal oxygen with standard oxygen therapy in 1472 infants under the age of 1 year with

bronchiolitis and an acute requirement for oxygen. Infants with an immediate need for respiratory support and admission to PICU were excluded, as were patients with cyanotic heart disease, airway obstruction and basal skull fracture. High-flow nasal oxygen was delivered at 2 L/kg/min via the AIRVO™2 device, aiming for a target SpO_2 of either 92% to 98% or 94% to 98%, depending on the institution. Standard oxygen therapy was delivered via nasal cannulae, with an oxygen flow rate up to a maximum of 2 L/min, aiming for a target SpO_2 of 92% to 98%. The primary outcome of an escalation of care due to treatment failure occurred in 12% of the high-flow group and 23% of the standard oxygen therapy group (risk difference, −11%; 95% CI, −15 to −7; P<0.001). There was no difference in duration of either oxygen therapy or hospital stay.

Although recommended in guidelines by both the WHO and the American Academy of Pediatrics, no direct evidence supports this strategy of targeting peripheral oxygenation saturation targets of >90%. BIDS[11] was a randomised controlled equivalence trial undertaken in 8 centres in the UK between 2012 and 2013 to test this approach. It compared giving supplemental oxygen when oxygenation saturation targets fell below 90% with giving supplemental oxygen when saturations were less than 94%. The pulse oximeters in the lower-target group were modified to show a true value of 90% as 94% to minimise bias. 615 infants, aged 6 weeks to 1 year, admitted to hospital with viral bronchiolitis, were recruited. Groups were similar at baseline, with a median SpO_2 of 95%, and approximately 40% having an SpO_2 ≤94%. Supplemental oxygen was delivered to 73% of the high-target group and 56% of the low-target group. The primary outcome of duration of cough was 15 days in both groups. Time to being fit for discharge (44.2 hours vs 30.2 hours; HR, 1.46; 95% CI, 1.23 to 1.73; P<0·0001) and time to actual discharge (50.9 hours vs 40.9 hours; HR, 1.28; 95% CI, 1·09 to 1·50; P=0·003) were both longer in the higher-target oxygen group. There were two deaths in the higher-target oxygen group and none in the lower-target group. Rates of other adverse events were similar.

The BOOST II trial[12] sought to determine the optimum target oxygenation range for preterm infants. Between 2006 and 2010, 2448 infants, aged less than 24 hours since birth and less than 28 weeks gestation, were recruited in centres in the UK (n=973) , Australia (n=1135) and New Zealand (n=340). They were randomised to target peripheral oximetry saturations of 85% to 89% (lower-target group, n=1224) or 91% to 95% (higher-target group, n=1224). The oximeters were modified by ± 3 percentage points, allowing both groups to aim for a visible range of 88% to 92%, whilst achieving the allocated target range. The pulse oximeter algorithm was revised halfway through the trial, after the recruitment of 1261 patients (51.5%). The trial was terminated early for safety reasons. Groups were similar at baseline. In the 1187 children managed with the revised algorithm, there was a higher rate of death before hospital discharge in the low-

target group (23.1% vs. 15.9%; RR, 1.45; 95% CI, 1.15 to 1.84; P=0.002). For those managed with the original algorithm, there was no statistically significant difference in death before hospital discharge (15.6% vs. 17.3%; RR, 0.90; 95% CI, 0.70 to 1.15; P=0.39). The pooled analysis also showed no statistically significant difference in death before hospital discharge between the two groups (19.5% vs. 16.6%; RR, 1.16; 95% CI, 0.98 to 1.37; P=0.09). In the total population, there were less cases of retinopathy of prematurity in the low-target group (10.6% vs. 13.5%; RR, 0.79; 95% CI, 0.63 to 1.00; P=0.045), but more cases of necrotizing enterocolitis (10.4% vs. 8.0%; RR, 1.31; 95% CI, 1.02 to 1.68; P=0.04). In a post-hoc, unadjusted analysis of all patients at a corrected gestational age of two years, the infants in the low-target group had an increased rate of both death and disability (48.1% versus 43.1%; RR, 1.11; 95% CI, 1.01 to 1.23; P=0.02), and death (21.2% versus 17.7%; RR, 1.20; 95% CI, 1.01 to 1.43; P=0.04).[13] In a prospective individual participant data meta analysis of all five trial from the Neonatal Oxygen Prospective Meta-analysis (NeOProM) Collaboration (n=4965), the primary composite outcome of death or major disability occurred at similar rates in both the low and high-target groups (53.5% vs 51.6%, respectively; RR, 1.04; 95% CI, 0.98 to 1.09; P= 0.21, I^2 = 14%).[14]

The randomised pilot OXY-PICU trial[15] investigated the feasibility of comparing peripheral oxygen saturation targets of 88% to 92% with > 94% in children aged between 38 weeks gestation and 16 years and receiving either invasive or non-invasive respiratory support with supplemental oxygen. 119 children were recruited from 159 children who met eligibility criteria. After randomisation, the oxygenation levels differed significantly between the groups; median SpO_2 94.9% (IQR, 92.6% to 97.1%) and 97.5% (96.2% to 98.4%). There were no significant differences in clinical outcomes between the lower and higher groups, respectively: median length of hospital stay, 5 days vs 6 days; median length of invasive ventilation, 3 days vs 3 days; ventilator-free days by day 30, 23.1 vs 22.8; PICU mortality, 7.4% vs 7.5%. The pilot trial concluded a large pragmatic trial was feasible, which may soon be ready for reporting.

McCollum undertook a superiority randomised controlled trial in 644 acutely hypoxaemic (SpO_2 < 90%) children with pneumonia in Malawi, aiming to show nasal bubble CPAP was superior to low-flow nasal cannula oxygen.[16] The trial took place in non-intensive care wards and without daily physician oversight. It was stopped early for futility, due to an increased risk of death in the CPAP group (17% vs 11%; RR, 1.52; 95% CI 1·02 – 2·27; p=0.036). There was also a higher incidence of adverse events in the bubble CPAP group, 3% vs 1%, including more deaths possibly attributable to aspiration in the CPAP group (4 vs 1).

Another randomised trial comparing bubble CPAP, HFNC and standard oxygen therapy in children aged less than 5 years with severe pneumonia and hypoxaemia, took place in Bangladesh.[17] Bubble CPAP was delivered at 5 L/min, starting at a CPAP level of 5 cm H_2O; standard low-flow nasal cannula was administered at 2 L/min; and HFNC flows were set between 2 L/kg/min up to the maximum of 12 L/min. The trial was stopped after the second interim analysis. 225 children had been randomised to low-flow nasal cannula (n=79), bubble CPAP (n=67) and HFNC (n=79). Less children had treatment failure in the bubble CPAP group than in the low-flow nasal cannula group (RR, 0.27; 99.7% CI, 0.07 – 0.99; P=0.0026), although there was no difference in treatment failure between patients in the bubble CPAP and HFNC group (RR, 0.50; 99.7% CI, 0.11 – 2.29; P=0.175). Less children died in the bubble CPAP group (n=3), than in the standard oxygen group (n=10; RR, 0.25; 95% CI, 0.07 – 0.89; p=0.022).

A recent systematic review and meta analysis[18] incorporating 21 randomised controlled trials, and 5342 children, evaluated the relative efficacies of standard oxygen therapy, CPAP, bilevel positive airway pressure (BiPAP) and HFNC in children with acute lower respiratory tract infection and a requirement for oxygen. CPAP was superior to oxygen therapy for reducing the risk of intubation (OR, 0.40; 95% CI, 0.16 – 0.90). Both CPAP (OR, 0.42; 95% CI, 0.19 – 0.81) and HFNC (OR, 0.51; 95% CI, 0.29 – 0.81) were also superior in reducing the risk of treatment failure, although the quality of evidence was low.

How should we support acutely hypoxaemic children with pneumonia?

The COAST trial requires replication with an adequately powered trial, but it appears that high flow nasal cannulae is a safe choice in hypoxaemic children, either with or without oxygen.

References

1. Oxygen [Internet]. Wikipedia. 2022 [cited 2022 Jun 8];Available from: https://en.wikipedia.org/w/index.php?title=Oxygen&oldid=1089852400

2. Thiemens MH. Oxygen origins. Nat Chem 2012;4(1):66–66

3. Grainge C. Breath of life: the evolution of oxygen therapy. J R Soc Med 2004;97(10):489–93

4. GARLAND J. The Boston Medical and Surgical Journal, 1828–1928. N Engl J Med 1928;198(1):1–13

5. Maitland K, Aceh S, Russell EC, Group FT. Mortality after fluid bolus in African children with sepsis. N Engl J Med 2011;365:1351–3

6. Maitland K, Olupot-Olupot P, Kiguli S, et al. Transfusion Volume for Children with Severe Anemia in Africa. N Engl J Med 2019;381(5):420–31

7. Maitland K, Kiguli S, Olupot-Olupot P, et al. Immediate Transfusion in African Children with Uncomplicated Severe Anemia. N Engl J Med 2019;381(5):407–19

8. Ramnarayan P, Richards-Belle A, Drikite L, et al. Effect of High-Flow Nasal Cannula Therapy vs Continuous Positive Airway Pressure Following Extubation on Liberation From Respiratory Support in Critically Ill Children: A Randomized Clinical Trial. JAMA 2022;327(16):1555–65

9. Peters MJ, Macharia W, Molyneux E. A COASTal view: where prior beliefs and uncertainty collide. Intensive Care Med 2021;47(5):591–3

10. Franklin D, Babl FE, Schlapbach LJ, et al. A Randomized Trial of High-Flow Oxygen Therapy in Infants with Bronchiolitis. N Engl J Med 2018;378(12):1121–31

11. Cunningham S, Rodriguez A, Adams T, et al. Oxygen saturation targets in infants with bronchiolitis (BIDS): a double-blind, randomised, equivalence trial. The Lancet 2015;386(9998):1041–8

12. Oxygen Saturation and Outcomes in Preterm Infants. N Engl J Med 2013;368(22):2094–104

13. BOOST-II Australia and United Kingdom Collaborative Groups, Tarnow-Mordi W, Stenson B, et al. Outcomes of Two Trials of Oxygen-Saturation Targets in Preterm Infants. N Engl J Med 2016;374(8):749–60

14. Askie LM, Darlow BA, Finer N, et al. Association Between Oxygen Saturation Targeting and Death or Disability in Extremely Preterm Infants in the Neonatal Oxygenation Prospective Meta-analysis Collaboration. JAMA 2018;319(21):2190–201

15. Peters MJ, Jones GAL, Wiley D, et al. Conservative versus liberal oxygenation targets in critically ill children: the randomised multiple-centre pilot Oxy-PICU trial. Intensive Care Med 2018;44(8):1240–8

16. McCollum ED, Mvalo T, Eckerle M, et al. Bubble continuous positive airway pressure for children with high-risk conditions and severe pneumonia in Malawi: an open label, randomised, controlled trial. Lancet Respir Med 2019;7(11):964–74

17. Chisti MJ, Salam MA, Smith JH, et al. Bubble continuous positive airway pressure for children with severe pneumonia and hypoxaemia in Bangladesh: an open, randomised controlled trial. Lancet 2015;386(9998):1057–65

18. Wang Z, He Y, Zhang X, Luo Z. Non-Invasive Ventilation Strategies in Children With Acute Lower Respiratory Infection: A Systematic Review and Bayesian Network Meta-Analysis. Front Pediatr [Internet] 2021 [cited 2022 Jun 8];9. Available from: https://www.frontiersin.org/article/10.3389/fped.2021.749975

O2-ICU

Gelissen H, de Grooth HJ, Smulders Y, Wils EJ, de Ruijter W, Vink R, et al. Effect of Low-Normal vs High-Normal Oxygenation Targets on Organ Dysfunction in Critically Ill Patients. A Randomized Clinical Trial. JAMA 2021;326(10):940-948

Introduction

Multiple trials[1–5] in the past decade have investigated oxygenation targets in critically ill patients in the ICU. Most have compared low-normal range with a higher normal range, with one specifically investigating hyperoxia in septic shock. The potentially harmful effects of hyperoxia have been highlighted across a range of different conditions, including myocardial infarction,[6] cardiac arrest,[7] stroke[8] and sepsis.[2]

When administered to produce a state of hyperoxia, supplemental oxygen produces a range of physiological effects,[9] both beneficial and deleterious. Advantageous features include vasoconstriction, leading to improved blood pressure and organ perfusion, antibacterial and antifungal properties, and enhanced tissue repair. Potentially deleterious effects from hyperoxia most notably affect the respiratory and central nervous systems The overall balance between these opposing effects is uncertain in the critically ill, although a trial[2] investigating the administration of 100% oxygen to patients with septic shock was terminated early for harm with this intervention. Whether a lesser threshold of hyperoxia was safe or harmful is unclear.

Synopsis

The O2-ICU trial examined the hypothesis that hyperoxia would potentiate pre-existing inflammation in a group of critically ill patients and that a low-normal PaO2 range would be superior. This was a stratified, parallel group, open label, randomised controlled trial comparing a lower target PaO_2 range of 8 to 12 kPa (60 to 90 mm Hg) with a higher target PaO_2 range of 14 to 18 kPa (105 to 135 mm Hg) in adult ICU patients. It ran in 4 centres in the Netherlands between 2015 and 2019. The trial was published in *JAMA* on August 31st, 2021.

Eligible patients were adults admitted to the ICU, expected to stay at least 48 hours, and with ≥ 2 systemic inflammatory response syndrome criteria. Exclusion criteria included ICU admission post elective surgery, severe pulmonary artery hypertension, severe acute respiratory distress syndrome, severe chronic obstructive pulmonary disease, conditions with a requirement for a higher target oxygenation, such as carbon monoxide poisoning, and a non-intubation order.

Screening took place at the time of ICU admission. Randomisation was via a central web-based system, using permuted blocks of 4 to 8, and stratified by age, gender and reason for admission.

Patients were entered into the trial within 12 hours of ICU admission. The target PaO_2 range was achieved via manipulation of the fraction of inspired oxygen (FiO_2) or positive end expiratory pressure (PEEP). Oxygen could be delivered via nasal cannulae, face mask, high-flow nasal oxygen or mechanical ventilator. The target range was to be maintained until day 14, ICU discharge or death, although it could briefly be altered during interventions, such as a tracheostomy. Monitoring was via intermittent arterial blood gas measurements and peripheral oxygen saturations.

The primary outcome was a ranking based on the nonrespiratory cumulative daily change in sequential organ failure assessment (SOFA) score, from day 1 to day 14, ($SOFA_{RANK}$). 385 patients were required to identify a difference of 0.33 standard deviations on the primary endpoint, with 80% power at a two-sided 5% significance level. Two interim analyses were planned.
9925 patients were screened, 574 were eligible and randomised, and 400 took part in the trial, with 205 allocated to low PaO2 group and 195 to the high PaO2 group. The excluded patients lacked informed consent within a 24 hour window. The median time from ICU admission to inclusion was 4 hours in both groups. Baseline characteristics were similar between the groups. The median patient age was 68 years, 65% were male, 70% were medical patients, approximately 35% had systemic infections and 33% had pneumonia. The median PaO2 was approximately 12 kPa, with a median FiO2 of 0.45 and median PEEP 8 cm H20. About 75% were requiring vasopressors and 75% were receiving either invasive or non-invasive mechanical ventilation.

The two groups separated well in terms of oxygen exposure, with median PaO2 values of 10.8 kPa and 12.8 kPa. The lower PaO2 group had more episodes of mild hypoxaemia and the higher group slightly more episodes of hyperoxaemia. There were similar rates of severe hypoxaemia between the two groups.

The median $SOFA_{RANK}$ score decreased by 35 points (IQR, −63 to 0) in the low PaO2 group and by 40 points (IQR, −76 to −4.5) in the high PaO2 group (median difference, 10; 95% CI, 0 to 21; P = 0.06). Secondary outcomes were considered exploratory, with no difference in patient-centred outcomes including duration of mechanical ventilation (3.4 vs 3.1 days; difference, -0.15; 95% CI, -0.88 to 0.47; P=0.59), length of ICU stay (3.9 days vs 4.6 days; difference, -0.34; 95% CI, -1.14 to 0.37; P=0.34) and day 90 mortality (35% vs 34%,; difference 1; 95% CI, -9 to 11; OR, 1.03; 95% CI 0.67 to 1.59; P=0.91. Adverse events were also similar between groups.

Critique

O2-ICU is the latest in range of recent trials comparing two different oxygenation targets in the ICU. This trial differs from the others in a couple of important ways; firstly, the trial included all patients in the ICU, whether they were receiving mechanical ventilation or not, and secondly, the primary outcome was an unfamiliar metric.

The premise for the O2-ICU trial was that hyperoxia would prove harmful, drive inflammation, and produce negative effects on the circulation, including vasoconstriction, decreased cardiac output and impaired tissue oxygenation. As such, a population of patients already with markers of inflammation, in the form of at least 2 criteria for SIRS, was recruited. However, despite achieving reasonable exposure to oxygen, with separation between the two groups in terms of their oxygenation, there were no between group differences in markers of circulatory function, including total noradrenaline dose (0.55 vs 0.60 mg/hr), cardiac cause of death (40% vs 39%), new myocardial infarction (2.9% vs 3.6%) and new stroke (0.5% vs 1.0%).

This apparent absence of effect could be due to a lack of attainment of the target PaO2 in the higher range group. The trial planned to compare target PaO2 ranges of 8 – 12 kPa with 14 – 16 kPa, but the actual oxygen range achieved by the high range was below the intended value, at a median of just 12.8 kPa. This impacts the internal validity of the trial somewhat, as what was planned to be tested wasn't actually tested, although in an intention-to-treat analysis, the ambition to treat remains the key factor. Whether achieving the intended oxygen ranges would have altered the outcomes is speculative, as there is little signal of effect from the available data. This would be consistent with the overall body of evidence in this field, which appears to reflect little, if any, effect on physiology from the target oxygen ranges being tested at present.

Another issue impacting the internal validity of the trial is the large number of patients randomised but not otherwise included in the trial. Of the 574 patients who were randomised, 174 were excluded due to a lack of consent being obtained within 24 hours. This creates a systematic bias with the trial – were these patients sicker and so family members were less likely to agree to participation in the trial? Just as with the previous point, the principle of intention-to-treat is relevant here, with almost one-third of the randomised cohort not contributing to the primary outcome. It was unclear in the manuscript how these patients were handled, and whether they were similar to the 400 analysed patients.

An important discussion point is the choice of primary outcome. The $SOFA_{RANK}$ score is an unfamiliar measure to clinicians and an unimportant one to patients. While the rationale for choosing this is well described in the O2-ICU manuscript, including

overcoming the competing risks of mortality and surrogate endpoints, the multiple issues with this are neatly laid bare in the accompanying editorial, including the measure relating to intra-group change rather than inter-group change, sensitivity to change in PaO2, including across the spectrum of PaO2, and interpretation. It is likely clinicians would default to more familiar and patient centric outcomes such as mortality, length-of-stay, and durations of organ support to guide their decision making.

The results of the trial should be generalisable to similar healthcare settings. Although the trial only ran in one country, the Netherlands, it included both academic and non academic centres. The algorithms for oxygenation were straightforward and the trial included allcomers to the ICU with markers of inflammation and an expected stay ≥ 48 hours. Multiple delivery systems for oxygenation were included, again broadening the scope for extrapolation. Monitoring was largely with arterial blood gas measurements, with medians of 4 to 6 samples taken per day per patient, again in keeping with usual practice.

Where this sits in the body of evidence

CLOSE[3] was an unblinded, pilot, parallel group, randomised controlled trial evaluating the feasibility of comparing a restrictive oxygenation strategy with a liberal oxygenation strategy in patients receiving invasive mechanical ventilation in the ICU for less than 24 hours and expecting to continue receiving this for an additional 24 hours. The restrictive group had a target SpO_2 of 88-92% and the liberal group a target SpO_2 ≥ 96%. The trial ran in 4 centres in 3 countries between 2013 and 2014. 52 patients were randomised to the restrictive oxygen group and 51 to the liberal oxygen group. The oxygenation targets for each group were achieved (mean SpO_2 93% vs 97%), confirming the feasibility of a larger trial. Oxygenation values were off target just 6% of the total time. There was no signal of harm with a restrictive approach. SpO_2 was < 88% just 1% of the time in the restrictive group and was > 98% 22% of the time in the liberal group. 90 day mortality was 40% and 37% in the restrictive and liberal groups, respectively (P=0.74).

OXYGEN-ICU[1] was an Italian, single centre, open-label, parallel group, randomised controlled trial comparing conservative and liberal oxygen therapy in patients expected to remain in the ICU for at least 72 hours. The conservative arm had their PaO_2 maintained between 70 and 100 mm Hg (SpO_2 94% to 98%) and the liberal group had theirs maintained up 150 mm Hg (SpO_2 97% to 100%). The trial was stopped early after an unplanned analysis, due to difficulties in recruitment, partly from the effects from an earthquake in the region and partly due to an anticipated loss of equipoise amongst nursing staff. 480 out of a planned 660 patients had been recruited. 434 patients were included in the modified intention-to-treat analysis. The conventional group had a higher daily time-weighted FiO_2 (median FiO_2, 0.39 vs 0.36) and median PaO_2, (102 mm Hg vs 87

mm Hg; P < 0.001). ICU mortality was lower in the conservative group; 11.6% vs 20.2% (difference, 8.6%; 95% CI, 1.7% to 15.0%; P=0.01). Hospital mortality was also lower in the conservative group (24% vs 33.9%; P=0.03), as was the proportion with liver failure (1.9% vs 6.4%, P=0.02), new episodes of bacteraemia (5.1 vs 10.1%; P=0.049) and mechanical ventilation free hours (72 vs 48; P=0.02).

ICU-ROX[4] was a 1000 patient pilot trial comparing a conservative oxygenation strategy, aimed at reducing oxygen exposure, with standard care. It took place in 21 ICUs in Australia and New Zealand between 2015 and 2018. Patients in the conservative arm were managed between SpO_2 values of 90% and 97%. The standard care arm had a lower SpO_2 limit of 90% and no upper limit. All adult patients being treated in the ICU with an expected length of stay until at least two days. The primary outcome was the number of ventilator-free days at day-28, and was similar in both groups; median duration 21.3 days vs 22.1 days in the conservative and liberal groups, respectively (difference -0.3 days; 95% CI, -2.1 to 1.6; P=0.80). Mortality at 180 days was also similar between the two groups, 35.7% vs 34.5%, respectively.

LOCO2[10] was a French multi-centre, open-label, randomised controlled trial which compared higher (PaO_2 target 90 to 105 mm Hg) and lower (PaO_2 target 55 to 70 mm Hg) oxygenation targets in patients with ARDS receiving invasive mechanical ventilation. 850 patients were required at identify a 9% reduction in 28 day mortality with the conservative oxygenation strategy, from a baseline of 30% in the liberal group to 21% in the conservative group. Both groups were managed with the same ventilatory protocol. The trial was stopped early, with 205 patients enrolled, after an interim analysis identified a low likelihood of achieving a significant difference in the primary outcome of mortality at day 28, and a signal of harm in the lower oxygenation group, due to an excess of cases of mesenteric ischaemia (5 vs 0). The primary outcome occurred in 34.3% of the lower oxygenation group and 26.5% of the higher oxygenation group, a difference of 7.8% (95% CI, −4.8 to 20.6). Mortality at day 90 was 44.4% in the conservative group and 30.4% in the liberal group (difference, 14%; 95% CI, 0.7 to 27.2)

HOT-ICU[5] was an international multi-centre randomised controlled trial comparing a target PaO2 of 60 mm Hg (n=1462) with 90 mm Hg (n=1466) in 2928 ICU patients with a requirement for a moderate degree of supplemental oxygenation. The trial ran between 2017 and 2020 at 35 ICUs in Denmark, Switzerland, Finland, the Netherlands, Norway, the United Kingdom, and Iceland. Groups were similar at baseline and separated well in terms of their oxygen exposure, with median (IQR) PaO_2 values of 62 (59 – 66) mm Hg and 76 (71 – 81) mmHg, in the lower and higher groups respectively. The administered median (IQR) FiO2 was correspondingly lower in the low PaO2 group at 0.45 (0.36 to 0.57) versus 0.59 (0.48 – 0.74). The primary outcome of death at 90 days occurred

similarly in both groups, at 42.9% and 42.4%, respectively (aRR,1.02; 95% CI, 0.94 to 1.11; P = 0.64). Secondary outcomes and adverse events were also similar between groups.

COAST[11] was an open-label fractional-factorial randomised controlled trial investigating oxygenation targets in African children with severe pneumonia. Depending on the baseline SpO_2, patients were enrolled into two strata, a hypoxaemic stratum (SpO_2 80 to 91%) and a severe hypoxaemic stratum (SpO_2 < 80%). In the hypoxaemic stratum, patients were randomised in a 1:1:2 fashion to either high flow nasal therapy (using either air or blended oxygen depending on the SpO_2; n=363), low flow oxygen (face mask or nasal cannulae; n=364) or permissive hypoxaemia (n=727). Patients in the severe hypoxaemic stratum were randomised to high flow nasal therapy (air or blended oxygen; n=194) or low flow oxygen (n=194). The target SpO_2 was ≥ 92% breathing room air. Patients in the permissive hypoxaemia group received low flow oxygen if their SpO_2 fell below 80%. The trial was stopped early after recruiting 1852 out of a planned 4200 children, due to recruitment difficulties. Adherence to the protocol was excellent and the primary outcome was recorded for almost all patients. Just 15% of the permissive hypoxaemia group required oxygen therapy. In the severe hypoxaemia stratum, the primary endpoint of mortality at 48 hours occurred in 9.3% receiving HFNT and 13.4% in the low flow oxygen group. In the hypoxaemic stratum, 48 hour mortality was 1.1% in the high flow group, 2.5% in the low flow oxygen, and 1.4% in the permissive hypoxaemia group. The primary analysis compared firstly, high flow therapy with low flow oxygen, and secondly, liberal therapy (high flow or low flow) with permissive hypoxaemia. The adjusted odds ratio for high flow therapy versus low flow oxygen was 0.60 (95% CI, 0.33 to 1.06; P=0.076) and for liberal therapy versus permissive hypoxaemia was 1.16 (95% CI, 0.49 to 2.74; P= 0.728).

HYPER2S[2] was a two-by-two factorial, open-label, multi-centre, randomised, clinical trial comparing hyperoxia (FiO2 1.0) with normoxia (FiO2 adjusted to achieve a SpO2 88% - 95%) and 3% hypertonic saline with 0.9% saline in patients with septic shock. The trial ran in 22 French ICUs between 2012 and 2014. Participants were randomly assigned 1:1:1:1 to the four groups, stratified by site and presence or absence of acute respiratory distress syndrome. The trial was terminated early for harm after the randomisation of 442 patients (normoxia, n=223; hyperoxia, n=219; isotonic, n=224; hypertonic, n=218). 43% of the hyperoxia group had died by by day 28 as compared with 35% of the normoxia group (HR, 1.27; 95% CI, 0.94 – 1.72; P=0·12). There were also more serious adverse events in the hyperoxia group, including more episodes of ICU-acquired weakness and atelectasis.

Should we target a low-normal PaO2 in critically ill patients?

Yes, while the absolute thresholds for harm or benefit with moderate hyperoxia are unclear, it is logical to aim for a low-normal PaO_2 value.

References

1. Girardis M, Busani S, Damiani E, et al. Effect of conservative vs conventional oxygen therapy on mortality among patients in an intensive care unit: the oxygen-ICU randomized clinical trial. JAMA 2016;316(15):1583–9.

2. Asfar P, Schortgen F, Boisramé-Helms J, et al. Hyperoxia and hypertonic saline in patients with septic shock (HYPERS2S): a two-by-two factorial, multicentre, randomised, clinical trial. Lancet Respir Med 2017;5(3):180–90.

3. Panwar R, Hardie M, Bellomo R, et al. Conservative versus liberal oxygenation targets for mechanically ventilated patients. A pilot multicenter randomized controlled trial. Am J Respir Crit Care Med 2016;193(1):43–51.

4. Mackle D, Bellomo R, Bailey M, et al. Conservative Oxygen Therapy during Mechanical Ventilation in the ICU. N Engl J Med 2020;382(11):989–98.

5. Schjørring OL, Klitgaard TL, Perner A, et al. Lower or Higher Oxygenation Targets for Acute Hypoxemic Respiratory Failure. N Engl J Med 2021;384(14):1301–11.

6. Stub D, Smith K, Bernard S, et al. Air Versus Oxygen in ST-Segment–Elevation Myocardial Infarction. Circulation 2015;131(24):2143–50.

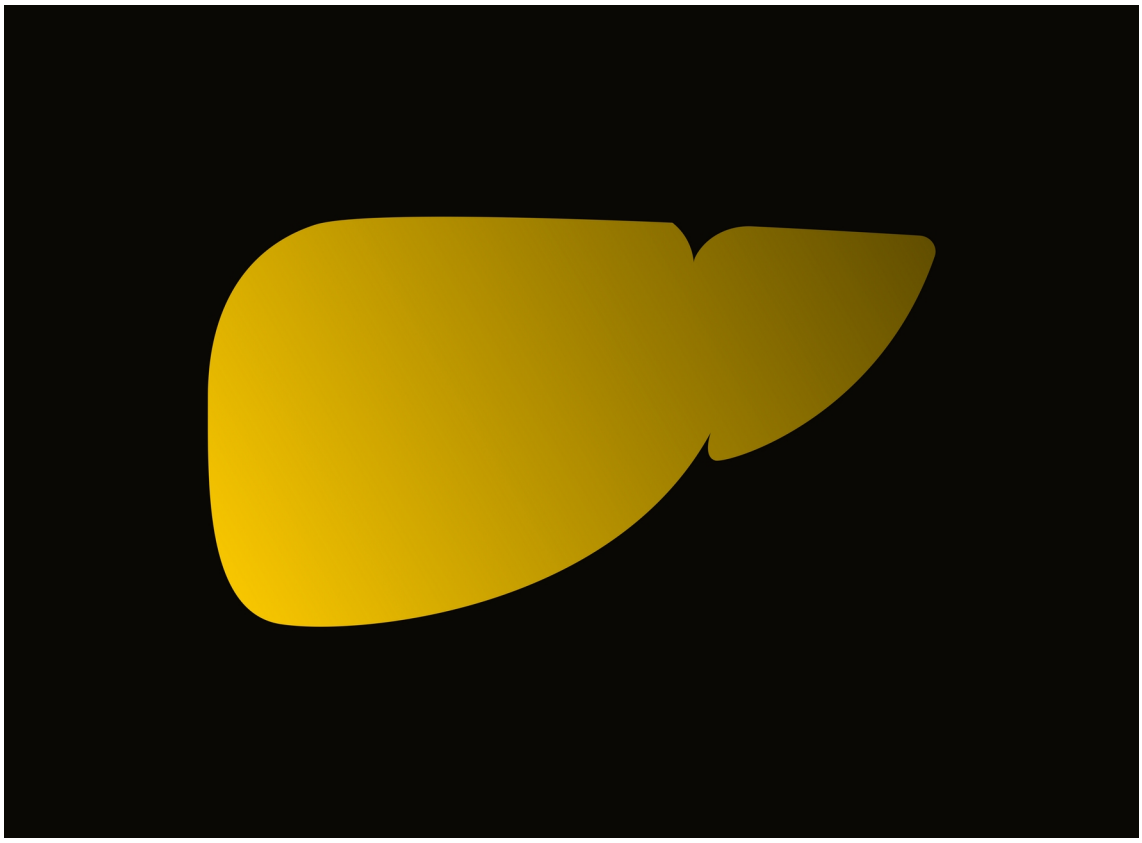
7. Kilgannon JH, Jones AE, Shapiro NI, et al. Association Between Arterial Hyperoxia Following Resuscitation From Cardiac Arrest and In-Hospital Mortality. JAMA 2010;303(21):2165–71.

8. Rincon F, Kang J, Maltenfort M, et al. Association between hyperoxia and mortality after stroke: a multicenter cohort study. Crit Care Med 2014;42(2):387–96.

9. Bitterman H. Bench-to-bedside review: Oxygen as a drug. Crit Care 2009;13(1):205.

10. Barrot L, Asfar P, Mauny F, et al. Liberal or conservative oxygen therapy for acute respiratory distress syndrome. N Engl J Med 2020;382(11):999–1008.

11. Maitland K, Kiguli S, Olupot-Olupot P, et al. Randomised controlled trial of oxygen therapy and high-flow nasal therapy in African children with pneumonia. Intensive Care Med 2021;47(5):566–76.



Liver Trials

CONFIRM

Wong F, Pappas SC, Curry MP, Reddy KR, Rubin RA, Porayko MK, et al. Terlipressin plus Albumin for the Treatment of Type 1 Hepatorenal Syndrome. N Engl J Med 2021;384:818-2

Introduction

Acute-on-chronic liver failure, the sudden decompensation of cirrhosis with associated organ failures,[1] has a global prevalence amongst patients admitted to hospital with decompensated cirrhosis of 35%, and a 90-day mortality rate of 58%.[2] Worldwide, alcohol is the most common underlying cause of such cirrhosis (45%), with infection being the most frequent precipitant of acute-on-chronic liver failure (35%) and acute kidney injury being the most prevalent organ failure (49%).[2] For patients with hepatorenal syndrome-acute kidney injury (HRS-AKI; previously termed type 1 hepatorenal syndrome),[3] 90 day survival without transplantation is approximately 45%.[4]

HRS-AKI has been defined as acute kidney injury, according to the International Club of Ascites-AKI criteria, in the presence of cirrhosis and ascites, with a lack of response to 2 consecutive days of diuretic withdrawal and plasma volume expansion with 1 g/kg of albumin, and the absence of shock, nephrotoxic drugs and structural kidney disease.[3] HRS-AKI had been thought of as a functional disorder, with splanchnic and systemic vasodilation reducing the effective circulation blood volume, triggering sodium and water retention, leading to ascites formation in the presence of portal hypertension. Intense renal vasoconstriction follows, due to activation of the renin-angiotensin-aldosterone, vasopressin and sympathetic systems, producing renal ischaemia.[5] Given the primacy of the splanchnic / systemic vasodilation, treatment with a vasopressor with effects on the splanchnic circulation is logical. Unfortunately, in the trials undertaken to date, despite improvements in renal function, no clear effect has been seen on mortality.[2] However, the trials to date were small, creating a knowledge gap which may be filled by a larger randomised controlled trial.

Synopsis

The CONFIRM trial[6] was a bi-national, multi-centre, stratified, parallel group, double-blind, randomised controlled trial comparing terlipressin and albumin with placebo and albumin in patients with type 1 HRS. The trial ran in 60 centres in the USA and Canada between in 2016 and 2019. It was published in the *New England Journal of Medicine* on March 4th 2021.

Eligible patients were adults with cirrhosis, ascites and a diagnosis of type 1 HRS based on the 2007 and 2015 International Ascites Club diagnostic criteria. Patients were

required to have rapidly progressive deteriorating renal function with a serum creatinine ≥ 2.25 mg/dL (199 µmol/L) and no sustained improvement in renal function at least 48 hours after diuretic withdrawal and the beginning of plasma volume expansion with albumin, defined as a sustained serum creatinine decrease of 20% or a decrease < 2.25 mg/dL. Patients were excluded if they had a serum creatinine level greater than 7 mg/dL (619 µmol/dL), one or more large volume paracentesis of ≥ 4 litres within 2 days of randomisation, sepsis or other uncontrolled bacterial infection, received less than 2 days of antimicrobial therapy for infection, were in shock, had received nephrotoxic agents within the previous 4 weeks, had an estimated life expectancy of less than 3 days, a superimposed acute liver injury other than acute alcoholic hepatitis, intrinsic renal disease, severe cardiovascular disease, renal replacement therapy within 4 weeks, ongoing use of vasopressors or transjugular intrahepatic portosystemic shunt within 30 days.

Patients were centrally randomised in a 2:1 ratio to the terlipressin group, stratified by a serum creatinine above or below 3.4 mg/dL (301 µmol/L) and large volume paracentesis within the previous 3 to 14 days.

The intervention group received 1 mg of terlipressin intravenously every 6 hours up to a maximum of 14 days. This was administered as a bolus injection over 2 minutes. The dose of terlipressin could be increased to 2 mg every 6 hours if the serum creatinine decreased by less than 30% by day 4 and after a minimum of 10 doses had been administered. Terlipressin was continued until 24-hours after the creatinine value was less than or equal to 1.5 mg/dL (133 µmol/L) or up to a maximum of 14 days. It was to be discontinued if the serum creatinine was maintained at or above the baseline value on day 4 and after a minimum of 10 doses have been administered. In addition, terlipressin was discontinued if the patient underwent renal replacement therapy, liver transplantation, TIPS, renal replacement therapy, or suffered cardiac or mesenteric ischaemia.

The control group received a visually identical placebo which was also reconstituted in 5 ml of saline and administered in the same fashion. Patients in both groups were recommended to receive albumin infusions at a dose of 1 g/kg to a maximum of 100 g on day 1, and 20 g to 40 g from day 2 onwards. Patients with a partial response to the study intervention (<30% reduction in serum creatinine), and who suffered a recurrence of type 1 HRS during the study follow-up period, could be retreated with the assigned intervention for a maximum of another 14 days.

The primary outcome measure was verified reversal of HRS, defined as two consecutive serum creatinine values ≤ 1.5 mg/dL at least 2 hours apart up to day 14, and survival

without renal replacement therapy for at least 10 more days. Therapeutic failure was classified as the receipt of renal replacement therapy, TIPS, or open label vasopressor therapy before day 14, lack of improvement in serum creatinine by day 4, or absence of serum creatinine decrease to less than 1.5 mg/dL by day 14, as well as discontinuation of the study intervention before clinical success was achieved. 300 patients were required to identify a 4.1% decrease in the rate of occurrence of the primary outcome from 12.5% in the control group to 8.4% in the intervention group with 90% power. Multiple imputation was used to allow for missing data. Analysis was performed on an intention-to-treat basis. One interim analysis was performed.

309 patients were eligible for the trial and 300 were randomised, 199 to the terlipressin group and 101 to the control group. Groups were similar at baseline. The mean patient age was 54 years, 59% were male, cirrhosis was due to alcohol misuse in 67% and non-alcoholic steatohepatitis in 22%. The mean arterial pressure was approximately 78 mm Hg, serum creatinine 3.5 mg/dL and Child-Pugh scores of 10.1. 83% of the terlipressin group received albumin at a mean total dose per person of 199 g over a median of 5 days. 91% of the control group received albumin infusions at a mean total dose of 239 g over a median of 5.5 days. Equal numbers of patients in both groups received midodrine or octreotide pre-intervention period. 7% of each group had dose interruptions due to adverse events and more patients in the terlipressin group had permanent discontinuation of the study drug due to adverse events (12% vs 5%)

The primary outcome of verified reversal of HRS occurred in 32% (n=63) of the terlipressin group and 17% (n=17) of the control group (P=0.006). Clinical failure occurred in 61% of the terlipressin group and 80% of the control group. Of the 4 prespecified secondary endpoints, all occurred at lower rates in the terlipressin group, three of which were statistically significant; HRS reversal (39% vs 18%; P<0.001), defined as a serum creatinine level <1.5 mg/dL during the first 14 days; HRS reversal without renal replacement therapy by day 30 (34% vs 17%; P = 0.001); HRS reversal amongst patients with systemic inflammatory response syndrome (37% vs 6%; P<0.001); and verified reversal of HRS without recurrence by day 30 (26% vs 17%; P = 0.08). Relatively less liver transplants had occurred by day 90 in the terlipressin group (23% vs 29%); however, more patients in the terlipressin group had died at this timepoint (51% vs 45%; 95% CI, -6 to 18). Additionally, although the overall incidence of adverse events was similar between the two groups (88% and 89%), as were the number of patients with a temporary cessation of their study drugs (7% each), the terlipressin group suffered more permanent cessations of study drug (12% vs 5%). There were also more serious adverse events in the interventional group, including gastrointestinal events and respiratory failure, with an excess of deaths due to respiratory disorders (11% vs 2%).

Critique

CONFIRM is the largest yet randomised placebo-controlled trial evaluating terlipressin for the treatment of HRS-AKI. It was sponsored by Mallinckrodt Pharmaceuticals, the company marketing Terlivaz®, the proprietary form of terlipressin in the USA, to support an application for regulatory approval.[7] Although licensced for use in HRS-AKI in Europe, and recommended for use in the clinical practice guideline for the management of patients with decompensated cirrhosis from the European Association for the Study of the Liver,[8] the supporting evidence is relatively weak.

The trial is comparable in design to the other major trials in this field, with similar dosing of terlipressin and albumin. The population and endpoints chosen for the trial were also analogous to those in the other studies. One issue noted in the accompanying editorial was that the serum creatinine level used to identify patients with HRS-AKI for entry into the trial differs from the current definition of HRS-AKI.[7] CONFIRM used a level of 2.25 mg/dL (199 µmol/L), rather than the current definition of a rise of >0.3 mg/dL (26 µmol/l) from baseline. Although, starting therapy at an earlier timepoint may have proven more efficacious, the design, and results, are consistent with the other evidence in the field.

Whilst the design of the trial is excellent, several points are worth considering in more detail. Firstly, the premise of the trial is based on the vasodilatory hypothesis of HRS-AKI, as described in the introduction.[9] However, the understanding of the mechanisms contributing to HRS-AKI continues to evolve past a simple concept of splanchnic vasodilation, ineffective circulating blood volume and intrinsic renal ischaemia. Although terlipressin is a vasopressin analogue with a specific vasopressor effect on the splanchnic circulation, numerous other processes not affected by terlipressin have been suggested to contribute to HRS-AKI, including cirrhotic cardiomyopathy, systemic inflammation, hepato-adrenal syndrome, bile cast nephropathy, intra-abdominal hypertension, and a complex neural hepatorenal reflex dependent on liver osmoreceptors, chemoreceptors, and baroreceptors.[10]

Despite a rationale of expanding the circulatory volume with albumin and reversing the vasodilatory state with terlipressin appearing sound, and which may be successful in treating HRS-AKI (which was the primary outcome), it is less clear if this impacts the overall trajectory of a patient with acute-on-chronic liver failure. Does the advanced state of liver impairment, with its relentless progression towards death, ultimately overwhelm any organ specific improvements seen in the kidney? The results of the three major trials in this field (CONFIRM,[6] OT-0401[11] & REVERSE[4]) all support this concept.

Although the intervention group demonstrated improved renal function without improved survival, there were signals of possible heterogeneity of effect, suggesting

subgroups for whom this treatment may be more effective. Five subgroups were examined post hoc, with three demonstrating benefit. Patients with alcoholic hepatitis (31% vs 8%), patients with a baseline serum creatinine between 3 and 5 mg/dL (28% vs 6%), and patients with systemic inflammatory response syndrome (26% vs 4%), all had higher incidences of verified reversal of HRS with terlipressin therapy, in contrast to placebo. However, those with serum creatinine values either > 5 mg/dL or below 3 mg/dL had little benefit. Patients with a baseline mean arterial pressure < 70 mm Hg also appeared to benefit (26% vs 4%), although the 95% confidence limits overlap between the terlipressin and placebo groups. Perhaps this reflects patients both sick enough (serum creatinine >3 mg/dL) to benefit, yet not too sick (serum creatinine < 5 mg/dL) to be unable to benefit, as well as identifying mechanisms of efficacy, with those with higher inflammatory measures improving with the anti-inflammatory effect of albumin in addition to vasopressor support, whilst those hypotensive were supported by the addition of a vasopressor alone.

The 20 additional cases of death due to respiratory failure seen in the terlipressin and albumin group (n=22) in comparison with the placebo group (n=2) is worrying. In the REVERSE trial, there was a slightly higher incidence of pulmonary oedema in the group receiving terlipressin (10.8% vs 7.4%). This phenomenon was also seen in the ATTIRE trial, investigating the maintenance of a serum albumin level above 30 g/L in hospitalised patients with cirrhosis (15 vs 4 patients). It may be that the combination of additional afterload on the left ventricle from vasopressin, combined with volume expansion from albumin, in a population with both ischaemic heart disease and cirrhotic cardiomyopathy, leads to pulmonary oedema, cardiopulmonary dysfunction and death. Interestingly, as mentioned, the placebo group received a greater volume of albumin, suggesting it is the combination of terlipressin and albumin, rather than albumin alone, which may be harmful in this trial. The administration of terlipressin to patients with cirrhosis is known to increase left ventricular afterload and end-diastolic volume, with resultant reduction in cardiac output and ejection fraction.[12]

Where this sits in the body of evidence

The small open-label TAHRS trial[13] compared terlipressin plus albumin (n=23) with albumin alone (n=23) in 46 patients with cirrhosis and HRS. Terlipressin was administered at a dose of 1 to 2 mg intravenously every 4 hours. In both groups, albumin was administered at a dose initially of 1 g/kg, followed by 20 to 40 g per day. The primary outcomes were improvement of renal function and survival at 3 months. Improvement of renal function was defined as complete (reduction in serum creatinine below 133 µmol/L) or partial (reduction in serum creatinine > 50% but with an end-of-treatment value ≥ 133 µmol/L). Renal function improved in 43% of patients in the terlipressin plus albumin group and 8.7% of patients in the albumin group. The median

time to improvement of renal function in the terlipressin and albumin group was 11 days. Survival at 3 months did not differ significantly between the two groups, 27% (terlipressin and albumin group) versus 19% (albumin group); P = 0.7. Amongst those in the terlipressin and albumin group, patients with type 2 HRS were more likely to achieve improvement in renal function than patients with type 1 HRS (67% vs 35%). Rates of adverse events were similar between the two groups.

Between 2004 and 2006, Sanyal and colleagues undertook the OT-0401 trial, which was a randomised, double-blind, placebo-controlled, multi-centre clinical trial in the USA, Germany and Russia. It compared terlipressin plus albumin (n=56) with placebo plus albumin (n=56) in 112 patients with acute or chronic liver disease and type 1 HRS.[11] Terlipressin was administered at a dose of 1 mg every 6 hours. This could be doubled after 4 days if the serum creatinine had not decreased by at least 30%. In both groups, albumin was administered at a dose of 100 g on day 1, and 25 g daily thereafter, up to a maximum of 14 days. The primary outcome was treatment success at day 14, defined as a serum creatinine level ≤1.5 mg/dL on 2 occasions at least 48 hours apart, without dialysis, death, or recurrence of type 1 HRS by day 14. Patients in the terlipressin plus albumin group (6.3 days) and placebo plus albumin group (5.8 days) received the study drugs for similar lengths of time. The primary outcome occurred in more patients in the terlipressin plus albumin group (25% vs 12.5%, P=0.093). More patients in the terlipressin plus albumin group also had reversal of their HRS, defined as a decrease in serum creatinine ≤1.5 mg/dL (34% vs 13%, P=0.008). Overall survival (42.9% vs 37.5%, respectively; P=0.839) and transplant-free survival to day 180 were similar between the two groups.

Published in 2016, the REVERSE study[4] also compared terlipressin plus albumin (n=97) with placebo plus albumin (n=99) in 196 patients with cirrhosis, ascites and type 1 HRS. This multi-centre, double-blind, parallel group, randomised controlled trial took place in 50 centres in the USA and 2 in Canada. Similar to the other trials, terlipressin was administered at a dose of 1 mg every 6 hours, and could be doubled to 2 mg on day 4 if the serum creatinine value had decreased by less than 30% of the baseline value. Albumin was administered to both groups at a dose of between 20 and 40 g per day. Study drugs could be discontinued after 4 days if the serum creatinine remained at baseline or higher. The study period was for up to 16 days. The primary endpoint was confirmed reversal of HRS, defined as 2 serum creatinine values of 1.5 mg/dL, at least 40 hours apart, whilst receiving treatment without renal replacement therapy or liver transplantation. Patients were similar at baseline. The primary outcome occurred in 19.6% of the terlipressin and albumin group and 13.1% of the placebo and albumin group (P=0.22). Hepatorenal syndrome reversal, defined as at least 1 serum creatinine value ≤ 1.5 mg/dL while on treatment was achieved in 23.7% of patients receiving

terlipressin and albumin and 15.2% of those receiving placebo and albumin (P=0.13). Overall survival and transplant-free survival were similar between groups. There were more ischaemic events in the terlipressin and albumin group.

Mohamed and colleagues performed a systematic review and meta analysis, incorporating 8 randomised controlled trials totalling 974 patients, comparing terlipressin plus albumin with albumin alone in patients with either type 1 or 2 HRS.[14] Of the included population, 61% of patients were male, their mean age was 55 ± 10 years, 56% had alcoholic liver disease, mean Child-Pugh score was 10.4 ± 1.8, mean arterial pressure was 76 ± 11 mm Hg, mean serum sodium 132 ± 6 mmol/L, mean serum creatinine 3.6 ± 1.2 mg/dL, mean serum albumin 3.4 ± 1 g/dL, and mean total bilirubin 13 ± 13 mg/dL. Compared with the placebo and albumin group, patients treated with terlipressin and albumin had a higher incidence of reversal of HRS (RR, 2.08; 95% CI, 1.51 to 2.86; P < 0.001) but no 90-day survival benefit (RR, 1.09; 95% CI, 0.84 to 1.43; P=0.52).

Should we routinely use terlipressin with albumin in patients with HRS-AKI?

The results of the CONFIRM trial, in addition to previous trials in the field, show this combination of interventions is effective in improving renal function, but not mortality. Further work is required to clarify their role.

References

1. Arroyo V, Moreau R, Jalan R. Acute-on-Chronic Liver Failure. N Engl J Med 2020;382(22):2137–45.

2. Mezzano G, Juanola A, Cardenas A, et al. Global burden of disease: acute-on-chronic liver failure, a systematic review and meta-analysis. Gut 2022;71(1):148–55.

3. Angeli P, Ginès P, Wong F, et al. Diagnosis and management of acute kidney injury in patients with cirrhosis: Revised consensus recommendations of the International Club of Ascites. J Hepatol 2015;62(4):968–74.

4. Boyer TD, Sanyal AJ, Wong F, et al. Terlipressin plus albumin is more effective than albumin alone in improving renal function in patients with cirrhosis and hepatorenal syndrome type 1. Gastroenterology 2016;150(7):1579-1589. e2.

5. Biggins SW, Angeli P, Garcia-Tsao G, et al. Diagnosis, Evaluation, and Management of Ascites, Spontaneous Bacterial Peritonitis and Hepatorenal Syndrome: 2021

Practice Guidance by the American Association for the Study of Liver Diseases. Hepatology 2021;74(2):1014–48.

6. Wong F, Pappas SC, Curry MP, et al. Terlipressin plus Albumin for the Treatment of Type 1 Hepatorenal Syndrome. N Engl J Med 2021;384(9):818–28.

7. Garcia-Tsao G. Terlipressin and Intravenous Albumin in Advanced Cirrhosis — Friend and Foe. N Engl J Med 2021;384(9):869–71.

8. Angeli P, Bernardi M, Villanueva C, et al. EASL Clinical Practice Guidelines for the management of patients with decompensated cirrhosis. J Hepatol 2018;69(2):406–60.

9. Schrier RW, Arroyo V, Bernardi M, Epstein M, Henriksen JH, Rodés J. Peripheral arterial vasodilation hypothesis: A proposal for the initiation of renal sodium and water retention in cirrhosis. Hepatology 1988;8(5):1151–7.

10. Simonetto DA, Gines P, Kamath PS. Hepatorenal syndrome: pathophysiology, diagnosis, and management. BMJ 2020;370:m2687.

11. Sanyal AJ, Boyer T, Garcia–Tsao G, et al. A randomized, prospective, double-blind, placebo-controlled trial of terlipressin for type 1 hepatorenal syndrome. Gastroenterology 2008;134(5):1360–8.

12. Krag A, Bendtsen F, Mortensen C, Henriksen JH, Møller S. Effects of a single terlipressin administration on cardiac function and perfusion in cirrhosis. Eur J Gastroenterol Hepatol 2010;22(9):1085–92.

13. Martín–Llahí M, Pépin M-N, Guevara M, et al. Terlipressin and albumin vs albumin in patients with cirrhosis and hepatorenal syndrome: a randomized study. Gastroenterology 2008;134(5):1352–9.

14. Mohamed MMG, Rauf A, Adam A, Kheiri B, Lacasse A, El-Halawany H. Terlipressin effect on hepatorenal syndrome: Updated meta-analysis of randomized controlled trials. JGH Open 2021;5(8):896–901.

ATTIRE

China L, Freemantle N, Forrest E, Kallis Y, Ryder SD, Wright G, et al. A Randomized Trial of Albumin Infusions in Hospitalized Patients with Cirrhosis. N Engl J Med 2021;384:808-17

Cirrhosis is characterised histologically by the presence of regenerative liver nodules and fibrotic tissue, in response to chronic liver inflammation.[1] It is a global problem, with an estimated 1 million deaths occurring annually, and is the third leading cause of death in adults aged 45 to 64 years.[1] Europe has the highest prevalence of heavy drinking in the world, with alcohol being the leading cause of cirrhosis in this continent.[2] 0.1% of the European population is estimated to have cirrhosis,[3] which causes almost 2% of all deaths in this region.[2] In the UK, over 3% of all critically ill patients admitted to the ICU in the UK have cirrhosis.[4] Hospitalised patients with cirrhosis are immunosuppressed, and over a quarter suffer a bacterial infection, with a resulting four-fold increase in mortality.[1] Patients with acute-on-chronic liver failure who develop a bacterial infection have a higher mortality than those without bacterial infection. Synthetic liver function is depleted as part of the general syndromes of cirrhosis and acute-on-chronic liver failure, contributing to lower plasma albumin levels than in healthy people.

Albumin is the most abundant plasma protein in the human body, with a total body pool of 250 g to 300 g for a 70 kg adult.[5] It is solely produced in the liver at a rate of 12 to 25 g/day. Approximately two-thirds of the body's albumin is stored in the extravascular space and one-third in the intravascular space. This ratio can change dramatically during critical illness, with up to a 300% increase of transcapillary movement during septic shock, resulting in increased losses due to transfer to non-exchangeable locations, such as the lumen of the gastrointestinal tract and wounds. Although albumin is well known for its oncotic effect, it also functions to bind and transport endogenous and exogenous compounds, maintains acid-base balance, has anticoagulant properties and supports microvascular function. A less obvious role is that of supporting the immune system.

The nature of the immunosuppression in patients with cirrhosis has been partly ascribed to an excess of Prostaglandin E2 (PGE_2).[6] This eicosanoid inhibits the secretion of cytokines from macrophages, with resultant decreased bacteria killing. Importantly, this effect is not seen in patients without cirrhosis. Albumin binds and inactivates PGE_2, potentially reversing this PGE_2 mediated immunosuppression, raising the possibility that exogenously administered albumin may prevent some of the excess infections, and deaths, seen in those with cirrhosis.

Synopsis

The ATTIRE (Albumin to Prevent Infection in Chronic Liver Failure) trial was a parallel group, open-label, multi-centre, stratified, randomised controlled trial evaluating a strategy of maintaining a serum albumin above 30 g/dL in hospitalised patients with decompensated cirrhosis. The trial ran in 35 UK centres between 2016 and 2019, and was published in the *New England Journal of Medicine* on March 4th, 2021.

Eligible patients were aged over 18 years, within 72 hours of being hospitalised for an acute decompensation of cirrhotic liver disease, and had a serum albumin level of less than 30 g/dL, with an expected duration of hospitalisation of at least 5 days. The main trial specific exclusion criteria were advanced hepatocellular carcinoma with a life expectancy of less than 8 weeks, those receiving palliative care and severe cardiac dysfunction.

Recruited patients were randomly allocated to either the intervention or control group in a 1:1 ratio, via an online service incorporating a minimisation algorithm. Patients were stratified by centre, MELD score, number of organ dysfunctions, serum albumin level and the use of antibiotics.

The intervention group received daily infusions of 20% human albumin solution, targeting a serum albumin level > 35 g/L, with the aim of achieving a level > 30 g/L. A tiered daily dosing regimen for albumin administration was suggested, with patients with a serum albumin level of 30 to 34 g/L receiving 100 ml 20% HAS; 26 to 29 g/L, 200 m 20% HAS; 20 to 25 g/L, 300 ml 20% HAS; and < 20 g/L, 400 ml 20% HAS. Albumin was administered for up to 14 days or discharge from hospital. The control group received standard care. Albumin administration was permissible for standard indications, such as large-volume paracentesis, spontaneous bacterial peritonitis, and hepatorenal syndrome.

The primary outcome was a composite of infection, renal dysfunction and death between days 3 and 15 post randomisation. The presence of an infection was adjudicated by the treating clinicians and supporting information sought for blinded validation by a panel of physicians. Renal dysfunction was defined as a 50% increase in serum creatinine from baseline or an absolute increase of 0.3 mg/dl (26.5 µmol/L), or the introduction of renal replacement therapy. With an expected incidence of the composite primary outcome of 30% in the control group, and a 10% attrition rate, 433 patients per group were required to identify a 30% reduction, from 30% to 21%, with 80% power at the 5% significance level. Analyses were performed on an intention-to-treat basis. The primary outcome was also assessed by stratum. Secondary outcomes included the individual components of the primary outcome, plus time to outcome, transplantation

within 6 months, and safety and tolerability of HAS, as well as several more and additional exploratory outcomes.

9273 patients were screened, 1563 were eligible, and 829 were randomised. One patient withdrew and 51 had more than one randomisation, leaving 777 patients for analysis , with 380 allocated to the albumin group and 397 to the control group. Groups were largely similar at baseline, although there were slightly more females in the albumin group (123 vs 104; 32% vs 26%) The mean patient age was 54 years, 97% were managed on a general ward, approximately 90% had alcohol excess as the cause of their cirrhosis, approximately 65% had worsening ascites as the reason for admission to hospital, albumin levels were similar between groups, as were measures of function the major organ systems. Patients were typically recruited on the day after hospital admission, with a mean (±SD) albumin level of 23.2 ± 3.7 g /L. Both groups were treated for similar durations of time: albumin group, median 8 days (IQR, 6 to 15) and control group, median 9 days (6 to 15).

Exposure to albumin differed significantly between the two group. Patients in the albumin group received more albumin (median 200 g vs 20 g; adjusted mean difference 143; 95% CI, 127 to 158 g). 49% of the control group received no albumin. The mean serum albumin level in the intervention group was 30 g/L for the intervention period.

The composite primary endpoint occurred in 29.7% of the albumin group and 30.2% of the control group (aOR, 0.98; 95% CI, 0.71 to 1.33; P = 0.87). The primary outcome did not differ when assessed according to strata. For the components of the primary endpoint, new infections occurred in 20.8% of the albumin group and 17.9% of the control group (aOR, 1.22; 95% CI, 0.85 to 1.75); renal dysfunction in 10.5% and 14.4%, respectively (aOR, 0.68; 95% CI, 0.44 to 1.11); and death in 7.9% and 8.3%, respectively (OR, 0.95; 95% CI, 0.56 to 1.59). Secondary outcomes occurred at similar rates in the two groups. At 6 months, 34.7% of the albumin group and 30.0% of the control group had died (aOR, 1.27; 95% CI, 0.93 to 1.73).

There were 87 serious adverse events in the albumin group and 72 in the control group, including more respiratory complications, with an excess of episodes of lung infection (15 vs 8) and pulmonary oedema (15 vs 4). However, there were less episodes of multi-organ failure in the albumin group (23 vs 31).

Critique

The ATTIRE trialists undertook an extensive programme to evaluate the effectiveness of albumin supplementation in hospitalised patients with cirrhosis. It started with an initial phase II feasibility study involving 400 patients. This confirmed both safety and the

incrementation of serum albumin with exogenous administration. This initial component included a stop/go assessment for progression to the phase 3 trial.

The ATTIRE trial raises fundamental questions about the efficacy of albumin in the management of patients with cirrhosis. The interventional group received ten times the dose of albumin as the control group, generating clear separation between groups in terms of exposure to the interventional agent. Albumin was also administered at an early time point, to maximise the likelihood of a beneficial effect occurring, should one exist. The trial also appears adequately powered to identify a potential effect, should it have occurred. Yet, not only was no beneficial effect seen, there were signals of harm from albumin administration, particularly affecting the respiratory system.

The premise of the trial is intriguing to consider, given the SAFE trial,[7] published 20 years ago, demonstrated no benefit from the addition of albumin to critically ill patients, regardless of their serum albumin level. Although there was a possible signal of improvement in those with severe sepsis in the SAFE trial (RR, 0.87; 95% CI, 0.74 to 1.02; P=0.09), the subsequent ALBIOS trial,[8] which directly investigated this subgroup, did not find superior outcomes with this strategy. Interestingly, in the ALBIOS trial, the subgroup with septic shock had better outcomes with albumin administration, but this requires further prospective study, being a subgroup effect found in a post hoc analysis. The recently published small FRISC trial[9] examined the administration of albumin in patients with cirrhosis and infection induced hypotension and found no short term benefits.

While the premise of the trial was to restore immune function with albumin in a group uniquely immunocompromised, the intervention also brings undesirable physiological stresses. The SAFE trial demonstrated that albumin has a superior volume expanding effect to saline, by a magnitude of 1.3:1. Portal hypertension is a significant complication of decompensated cirrhosis, often culminating in life-threatening upper gastrointestinal bleeding. In a Spanish multi-centre randomised controlled trial[10] in this condition, a liberal transfusion threshold was inferior to a more conservative threshold, with the mechanism thought to be increased portal pressure from a higher volume of transfusion. In ATTIRE, amongst the 24 patients suffering an adverse event with a gastrointestinal bleed, 7/11 of the patients in the albumin group had an initial variceal bleed, compared with 3/13 patients in the control group.

It is likely that, in a population of patients with cirrhosis who are not actively bleeding, the heart may be the most vulnerable organ to suffer from a relative state of volume overload. This is probably due to cirrhotic cardiomyopathy, present in 60% of patients with cirrhosis,[11] which impedes systolic and diastolic dysfunction, as well as

electrophysiological function. Both the ATTIRE and CONFIRM[12] trials reported an excess of pulmonary oedema or respiratory failure in those receiving albumin, but no difference in the other main mediators of decompensation, namely, hepatic encephalopathy, acute kidney injury-hepatorenal and syndrome, and spontaneous bacterial peritonitis.

Deaths occurring within two days of entry into the study were excluded from the analysis *a priori,* which reduces the possibility of immediate harm from albumin being recognised. Benefit from the intervention would carry over into the trial period from days 3 to 15 (no infection or renal impairment and ongoing survival), while harm arising from the trial intervention resulting in death, such as volume overload presenting as pulmonary oedema, heart failure, venous congestion induced acute kidney injury, would potentially be unmeasured in the death component of the composite primary outcome.

Where this sits in the body of evidence

The Italian ANSWER trial[13] was an investigator-initiated, multi-centre, randomised, parallel, open-label, pragmatic trial examining the long-term administration of albumin in patients with decompensated cirrhosis. 440 patients with cirrhosis and uncomplicated ascites were randomised to receive either 40 g of human albumin solution twice weekly for 2 weeks, and then 40 g weekly, for up to 18 months, or standard care. The serum albumin level rose from 31 g/L to 40 g/L in the albumin group, and remained unchanged in the control group. Amongst the 431 analysed patients, 18 month survival was significantly higher in the group receiving albumin, 77% vs 66% (HR, 0.62; 95% CI, 0.40 to 0.95). Non-liver related adverse events occurred at similar rates - 22% each.

ALB-CIRINF[14] was a French open-label, multi-centre, randomised controlled trial in 193 consecutive patients admitted to hospital with cirrhosis and sepsis. Participants were blindly allocated to receive antibiotics with 20% human albumin solution, at a dose of 1.5 g/kg on day 1 and 1 g/kg on day 3, or antibiotics alone. The primary outcome was the rate of renal failure at three months and occurred in 14.3% of the albumin group and 13.5% of the control group (P=0.88). The albumin group were slower to develop renal failure (mean 29.0 ± 21.8 vs. 11.7 ± 9.1 days, P = 0.018). Mortality at three months was similar (albumin group, 70.2% vs. control, 78.3%; P = 0.16). More patients developed pulmonary oedema in the albumin group, prompting the early termination of the trial.

Guevara[15] and colleagues also undertook a parallel group randomised controlled trial comparing antibiotics with or without albumin in 110 patients with cirrhosis and infections other than spontaneous bacterial peritonitis. Human albumin solution was administered at a dose of 1.5 g/kg on day 1 and 1 g/kg on day 3. The use of antibiotics was protocolised. Albumin was only administered to the control group for the management of type 1 hepatorenal syndrome. Groups were similar at baseline, except

for a lower mean serum sodium in the albumin group (129 vs 132 mmol/L). Infection resolved in the majority of patients (94%) and was equal between the two groups. There was no difference in the unadjusted primary outcome of survival at 3 months (albumin group, 82.6% vs control group, 80.4%). In a per protocol adjusted analysis, those receiving albumin had a superior three month survival (HR, 0.294; 95% CI, 0.091 to 0.954; P=0.04)

In 1999, Sort and colleagues compared the administration of cefotaxime with or without the addition of human albumin solution in 126 patients with cirrhosis and spontaneous bacterial peritonitis.[16] Human albumin solution was given at a dose of 1.5 g/kg on day 1 and 1 g/kg on day 3. The dose of cefotaxime was adjusted according to renal function. Groups were similar at baseline. 61 of the 63 patients in the cefotaxime plus albumin group received their assigned albumin. Both groups had similar rates of resolution of sepsis (>90%). The primary outcomes were the development of renal impairment and mortality. Renal impairment occurred in 33% of the cefotaxime only group and 10% of the cefotaxime and albumin group (P=0.01). Three month mortality was 41% and 22%, respectively (P=0.03).

The Albumin Italian Outcome Sepsis trial (ALBIOS),[8] published in 2014, followed on from the SAFE trial, and investigated the subgroup effect of improved mortality in patients with severe sepsis seen in this trial from the ANZICS group. This large Italian trial in 100 ICUs evaluated maintaining a serum albumin level > 30 g/L in critically ill adult patients in the ICU. 1810 patients were randomised and analysed, 903 in the albumin group and 907 in the control group. Groups were similar at baseline, with median SOFA scores of 8, approximately 80% receiving mechanical ventilation and 62% being in a state of shock. The albumin group received significantly more albumin and had a higher serum albumin level. There was no difference in the primary outcome of 28-day mortality; albumin group, 31.8% vs control, 32.0% (RR, 1.00; 95% CI, 0.87 to 1.14; P = 0.94).

The recent single-centre, open label randomised FRISC trial[9] compared saline with albumin for resuscitation in 308 cirrhotic patients with sepsis induced hypotension. Participants received either a 250 ml bolus of 5% HAS over 15 to 30 minutes, followed by 50 ml/hr over the next 3 hours, or a 30 ml/kg bolus of 0.9% saline over 15 to 30 minutes, followed by 100 ml/hr of saline over the next 3 hours. The primary outcome was the reversal of hypotension, defined as an increase in mean arterial blood pressure above 65 mm Hg at 3 hours. Groups were similar at baseline, with patients having an average mean arterial pressure of 53 mm Hg. More patients in the albumin group had a reversal of their hypotension at 3 hours, 11% vs 3.2% (OR, 3.9; 95% CI, 1.42 to 10.9; P=0.008). Mortality was also lower in the albumin group at 1 week; 43.5% vs 38.3%; P=0.03.

The American College of Gastroenterology issued updated guidelines[17] in February 2022 on the management of patients with acute-on-chronic liver failure. A strong recommendation, based on moderate quality evidence, was issued recommending not to use albumin infusions to maintain a serum albumin level > 30 g/L with the aim of preventing renal dysfunction, infections or death.

Should we target a serum albumin level > 30 g/L in hospitalised patients with cirrhosis?

No. The ATTIRE trial identified an increase in adverse events with no improvement in outcomes with this strategy

References

1. Ginès P, Krag A, Abraldes JG, Solà E, Fabrellas N, Kamath PS. Liver cirrhosis. The Lancet 2021;398(10308):1359–76

2. Blachier M, Leleu H, Peck-Radosavljevic M, Valla D-C, Roudot-Thoraval F. The burden of liver disease in Europe: A review of available epidemiological data. J Hepatol 2013;58(3):593–608

3. Acevedo J, Fernández J. New determinants of prognosis in bacterial infections in cirrhosis. World J Gastroenterol WJG 2014;20(23):7252–9

4. McPhail MJ, Parrott F, Wendon JA, Harrison DA, Rowan KA, Bernal W. Incidence and outcomes for patients with cirrhosis admitted to United Kingdom critical care units. Crit Care Med 2018;46(5):705–12

5. Nicholson JP, Wolmarans MR, Park GR. The role of albumin in critical illness. Br J Anaesth 2000;85(4):599–610

6. O'Brien AJ, Fullerton JN, Massey KA, et al. Immunosuppression in acutely decompensated cirrhosis is mediated by prostaglandin E2. Nat Med 2014;20(5):518–23

7. The Safe Study Investigators. A Comparison of Albumin and Saline for Fluid Resuscitation in the Intensive Care Unit. N Engl J Med 2004;350(22):2247–56

8. Caironi P, Tognoni G, Masson S, et al. Albumin Replacement in Patients with Severe Sepsis or Septic Shock. N Engl J Med 2014;370(15):1412–21

9. Philips CA, Maiwall R, Sharma MK, et al. Comparison of 5% human albumin and normal saline for fluid resuscitation in sepsis induced hypotension among patients with cirrhosis (FRISC study): a randomized controlled trial. Hepatol Int 2021;15(4):983–94

10. Villanueva C, Colomo A, Bosch A, et al. Transfusion strategies for acute upper gastrointestinal bleeding. N Engl J Med 2013;368(1):11–21

11. Razpotnik M, Bota S, Wimmer P, et al. The prevalence of cirrhotic cardiomyopathy according to different diagnostic criteria. Liver Int Off J Int Assoc Study Liver 2021;41(5):1058–69

12. Wong F, Pappas SC, Curry MP, et al. Terlipressin plus Albumin for the Treatment of Type 1 Hepatorenal Syndrome. N Engl J Med 2021;384(9):818–28

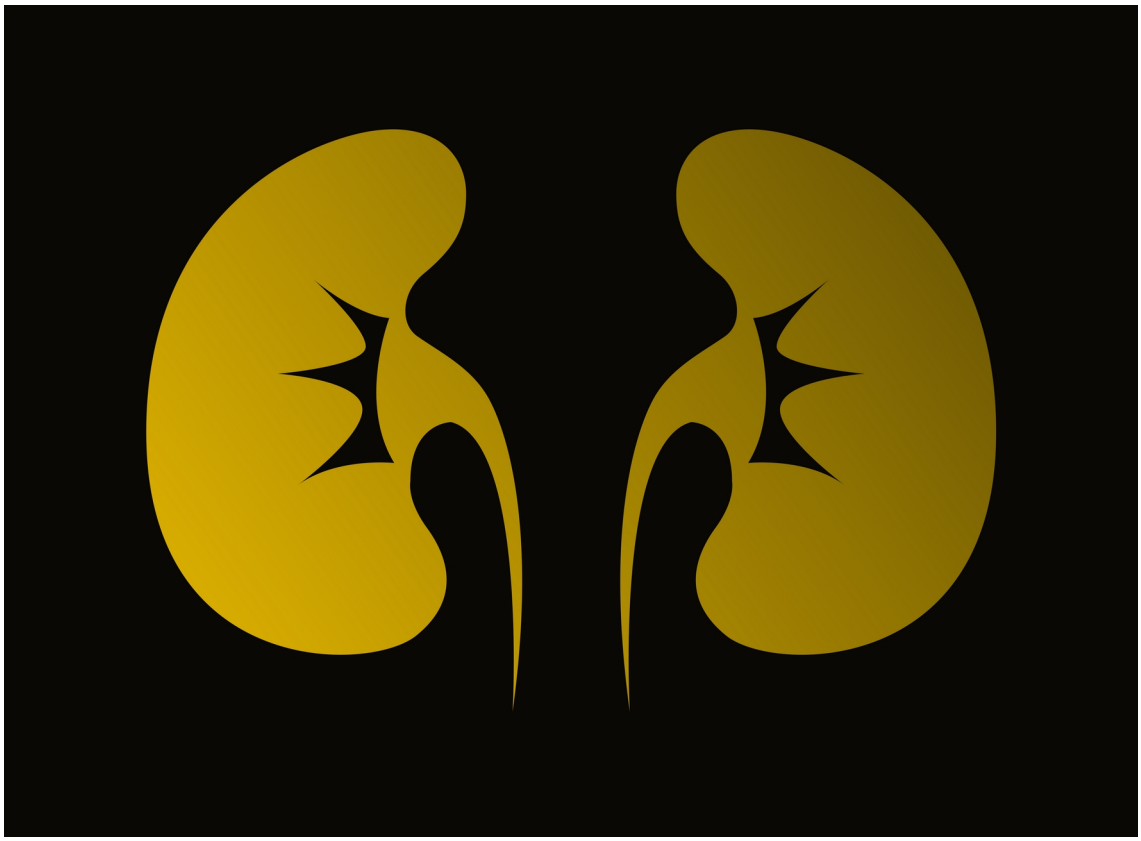
13. Caraceni P, Riggio O, Angeli P, et al. Long-term albumin administration in decompensated cirrhosis (ANSWER): an open-label randomised trial. Lancet 2018;391(10138):2417–29

14. Thévenot T, Bureau C, Oberti F, et al. Effect of albumin in cirrhotic patients with infection other than spontaneous bacterial peritonitis. A randomized trial. J Hepatol 2015;62(4):822–30

15. Guevara M, Terra C, Nazar A, et al. Albumin for bacterial infections other than spontaneous bacterial peritonitis in cirrhosis. A randomized, controlled study. J Hepatol 2012;57(4):759–65

16. Sort P, Navasa M, Arroyo V, et al. Effect of intravenous albumin on renal impairment and mortality in patients with cirrhosis and spontaneous bacterial peritonitis. N Engl J Med 1999;341:403–9

17. Bajaj JS, O'Leary JG, Lai JC, et al. Acute-on-Chronic Liver Failure Clinical Guidelines. Off J Am Coll Gastroenterol ACG 2022;117(2):225–52



Renal Trials

AKIKI2

Gaudry S, Hajage D, Martin-Lefevre L, Lebbah S, Louis G, Moschietto S et al. Comparison of two delayed strategies for renal replacement therapy initiation for severe acute kidney injury (AKIKI 2): a multicentre, open-label, randomised, controlled trial. Lancet 2021;397(10281):1293-1300

Introduction

Severe acute kidney injury is a common pathology in critically ill patients and an independent risk factor for mortality.[1] Renal replacement therapy (RRT) is initiated to support the failing kidney. In patients with life threatening complications of acute kidney injury (AKI) refractory to medical treatment (eg hyperkalaemia, metabolic acidosis, uraemic complications or fluid overload), there is a clear indication to initiate RRT. In the absence of such life-threatening complications, however, even in severe AKI, uncertainty remains as to how long RRT can be postponed without increasing harm.[2]

The proposed physiological benefits of early RRT initiation include eliminating toxins, maintaining electrolyte balance, modulating cytokine levels and avoiding hypervolaemia[2]. However, the majority of randomised trials thus far have shown that a strategy of early RRT initiation does not confer any survival benefit compared with delayed initiation in the absence of life-threatening complications of AKI.[3-5] RRT is an expensive resource and exposes the patients to the risks of anticoagulation, large bore central venous access and haemodynamic instability. Moreover, AKI will often resolve as the underlying cause is addressed. The longer RRT is safely delayed, therefore, the fewer the patients who ultimately receive the treatment.

In a previous publication, the Artificial Kidney Initiation in Kidney Injury (AKIKI) trial, in patients who met severe AKI cr881iteria, a delay of up to 72 hours in RRT initiation was not associated with any difference in mortality compared to early RRT initiation[4]. The AKIKI 2 trial investigated the effect of delaying RRT beyond 72 hours in patients fulfilling criteria for severe acute kidney injury[6].

Synopsis

The AKIKI 2 study was a multi-centre, open-label, two-arm, randomised controlled trial in 39 intensive care units in France and compared two strategies of delayed RRT initiation.

Eligible patients were adults, aged 18 years or older, hospitalised in the ICU who met KDIGO stage 3 AKI criteria (Kidney Disease; Improving Global Outcomes Classification) and who were receiving invasive mechanical ventilation, catecholamine infusion, or both. Patients fulfilled KDIGO stage 3 if they met any one of the following criteria; serum

creatinine 3 times baseline, serum creatinine ≥ 354 μmol/L, urine output < 0.3 ml/kg for > 24 hours or anuria for ≥ 12 hours. Patients were monitored for occurrence of one of the following to fulfil randomisation criteria: oliguria or anuria (urine output <0.3 mL/kg/hr or <500 mL day) for more than 72h or blood urea nitrogen (BUN) concentration between 112 mg/dL and 140 mg/dL (serum urea concentration between 40 mmol/L and 50 mmol/L). If patients met criteria for immediate dialysis hyperkalaemia (potassium > 6 mmol/L or > 5.5 mmol/L after medical treatment), metabolic acidosis (pH < 7.15) or diuretic-resistant pulmonary oedema), they were excluded from the trial.

Randomisation and blinded allocation occurred via a central web-based system, in a 1:1 ratio to each group using variable sized blocks. It was also stratified by centre.

If inclusion criteria were met, patients were randomised to either a delayed or more-delayed strategy. In the delayed strategy, RRT was to be commenced within 12 hours of fulfilling randomisation criteria. In the more-delayed strategy, RRT was postponed until they either developed one of the indications for immediate dialysis, or if BUN reached 140 mg/dL (urea 50 mmol/L) for one day. Management of RRT, including choice of modalities, anticoagulation method and device settings, was left to the discretion of treating clinicians at each study site. RRT discontinuation was recommended if diuresis was more than 1000 ml/24h spontaneously or more than 2000 mL/24h with the aid of diuretics. .

The primary outcome was the number of RRT-free days between randomisation and day 28. Secondary outcomes were mortality at ICU and hospital discharge, at day 28 and 60, the percentage of patients receiving RRT at least once, the number of patients with recovery of renal function between randomisation and day 60, the reason for initiation of RRT and the complications potentially related to acute kidney injury or RRT, amongst others.

On the basis of the original AKIKI trial, it was assumed there would be 17 RRT-free days in the delayed group, and this would increase to 21 days in the more-delayed strategy. To detect this difference with 80% power at a two-sided 5% significance level, assuming a 5% drop-out rate, the total sample size required was 270. The primary outcome was described by the median and compared using Wilcoxon rank-sum test.

5336 patients with AKI, on mechanical ventilation or catecholamine infusion, or both, were screened. 767 patients met KDIGO stage 3 acute kidney injury criteria and were monitoring for occurrence of randomisation criteria. 489 patients were excluded due to either being enroled in error, fulfilling criteria for urgent RRT, or not meeting randomisation criteria. 137 patients were randomly assigned to the delayed RRT

strategy and 141 patients to the more-delayed RRT strategy. Demographic, physiological and biochemical indices were similar between groups at baseline, albeit with a slightly higher incidence of vasopressor support in the delayed group compared to the more delayed group (69% vs 57%).
With the delayed strategy, 98% received RRT, with a median time of 3 hours from randomisation. With the more-delayed strategy, 79% of patients received RRT, with a median time of 33 hours from randomisation. Notably intermittent haemodialysis was used more frequently than continuous techniques as the initial RRT modality in both groups.

For the primary outcome, the median (IQR) number of RRT-free days did not differ significantly between the delayed strategy and the more-delayed strategy {12 days (0-25) vs 10 days (0-24); P=0.93}. 60-day mortality did not differ significantly between groups; (44% in the delayed strategy vs 55% in the more-delayed strategy; P= 0.071). However, in a prespecified multivariate analysis which adjusted for risk factors such as severity of illness and mechanical ventilation, the more-delayed strategy was associated with a higher 60-day mortality (HR, 1·65; 95% CI, 1·09 – 2·50). Other secondary outcomes did not differ between delayed and more-delayed strategies; for example, RRT dependence at day 60 (3 vs 1; p=0.62) and length of ICU stay (18 days vs 16 days, P=0.64) were both similar between groups. Moreover, there was no significant between-group difference in the incidence of complications potentially related to AKI or RRT.

Critique

The AKIKI 2 investigators sought to answer an important clinical question; how long is it safe to delay the initiation of RRT? The study has numerous strengths in its design, building on previous randomised control trials in this area.[3-5] The control, or delayed strategy, has already been found to be safe in the previous multi-centre AKIKI study.[4] The logical next step to address the question of 'how late is too late?' was therefore to randomise patients to further postponement of RRT from that which had already been shown to be safe. It must be noted, however, the study cohort was highly selective and of the 5336 screened for participation, only 278 patients met criteria for inclusion and randomisation, and more than 1000 patients were treated with RRT outside the randomisation period.

The study, therefore, focused on a specific and relatively stable group of patients with KDIGO stage 3 AKI. Nevertheless, the demographics of the patient cohort included in the AKIKI 2 trial were representative of most ICUs in high-income countries; the mean age was 65, of whom 56% had pre-existing hypertension. Furthermore, vasopressor use, biochemical data and presence of mechanical ventilation were similar to the STARRT-AKI trial, suggesting external validity of the results.[3] The main difference was the prevalence

of chronic kidney disease (CKD) in the AKIKI 2 cohort; 10% prevalence in AKIKI 2 vs 45% in STARRT-AKI. Pre-existing CKD is an independent risk factor for RRT dependence following AKI and may explain the relatively low numbers of RRT dependence at day 60 in both the delayed and more-delayed cohorts (4% vs 2%, respectively).[7]

The primary outcome of the AKIKI 2 trial was RRT-free days. All the previous studies have used 90 day mortality as the primary outcome, and studies have been powered to reflect this outcome.[3-5, 8] As a consequence, the AKIKI 2 sample size was relatively small compared to that in previous trials which compared RRT initiation timings. The trialists point out that the number of RRT-free days in the more-delayed strategy was shorter than that reported in the original AKIKI trial which provided the basis for the power calculation (12 days rather than 17)[6]. As a result, AKIKI 2 was underpowered, which may explain the absence of a significant difference for the primary outcome.

The protocol for AKIKI 2 suggested that RRT discontinuation should be considered in both groups if diuresis was greater than 500 mL/24 hours. If diuresis was greater than 1000 mL/24hr, discontinuation was recommended. By using RRT-free days as a primary outcome, there is a risk that with the lack of consensus criteria or prescriptive guidelines for discontinuing RRT, the number of RRT-free days will have been influenced by clinical decision-making by the treating team. This in turn could potentially have been influenced by group assignment, in that there could have been greater reluctance to discontinue RRT in a patient whose RRT has started later.

A strength of the study is the applicability of the protocol to real world practice. Whilst the criterion for initiation in larger studies such as STARRT AKI included oligoanuria and a BUN >40 mmol/L, AKIKI 2 removed oliguria as an indicator for RRT initiation.[3] There was a higher threshold of BUN to > 140 mg/dL before RRT was initiated. Together this allowed a test of the practicality and safety on an extension of the delay of initiation in the present study. It also, in some way, is more replicable of actual clinical practice as there are no formal criteria indicating the degree or duration of oliguria that should prompt initiation of RRT.

Contrastingly, and similar to AKIKI, AKIKI 2 did not standardise RRT modality, settings or anticoagulation. Indeed, in contrast to much of the established practice within the UK and many other countries, intermittent RRT was more commonly used than continuous RRT on the first day of RRT (60% in the delayed group versus 58% in the more-delayed group). Thus far, small randomised trials have failed to show any differences in mortality or renal outcomes when intermittent and continuous RRT have been compared.[9-11] No information is given on effluent dose or type of anticoagulation strategies, and thus it is difficult to make a judgment on external validity.

In summary, the AKIKI 2 trial did not show further postponement of RRT in this cohort to be of any benefit; rather it was associated with potential harm. While there were no major flaws in the methodology of the trial, the trial was underpowered for the primary outcome. Furthermore, the trial illustrates the lack of reliable tools to predict whether a patient with severe AKI will need RRT, and at what stage it should be initiated.[12]

Where this sits in the body of evidence

When to initiate RRT in patients with AKI has been a subject of much controversy over the last two decades, and although a definitive answer has not yet been forthcoming, recent trials have demonstrated the safety of a 'watch and wait' approach. Initially, Bouman and colleagues in 2002 randomised a total of 106 ventilated patients with oliguria to early high volume haemofiltration, early low volume haemofiltration or late low volume haemofiltration and reported that survival and recovery of renal function at 28 days were not improved by the early initiation of RRT.[13]

Contrastingly, and more recently, in 2016 the ELAIN study contraindicated these findings.[14] This was a single-centre study involving 231 critically ill patients with KDIGO AKI stage 2. Patients were randomised to early RRT (commenced within 8 hours of KDIGO stage 2) or delayed RRT (commenced within 12 hours of KDIGO stage 3). All 112 patients in the early group and 108 / 119 patients in the delayed group underwent RRT. The median time to initiation was 6 hours for the early group and 25.5 hours for the delayed group. The 90-day mortality was 39.3% in the early group compared with 54.7% in the delayed group (HR, 0.66; 95% CI, 0.45 to 0.97; P=0.03).[14]

In the same year, the first AKIKI study was published. In this multicentre study, 620 patients were randomised to either RRT at the onset of KIDGO stage 3 AKI, or to a strategy where RRT was only commenced if (1) a life-threatening complication of AKI developed, (2) serum urea was >40 mmol/L or (3) oliguria persisted for >72 hours following randomisation.[4] The primary outcome, survival at 90 days, was similar between both groups (48.5% vs 49.7%). Within the delayed group, only 51% of the cohort eventually required RRT.

IDEAL-ICU was another multi-centre randomised trial were 488 patients who fulfilled renal failure criteria (RIFLE classification) underwent either RRT initiated within 12 hours of randomisation or delayed for 48 hours after randomisation and only commenced in the absence of kidney recovery.[5] Similar to AKIKI, the primary outcome of 90-day mortality was similar in both arms (58% vs 54%), and 38% of those in the delayed arm avoided RRT.

STARRT-AKI is the largest randomised control trial to date to address the timing of RRT initiation.[3] 2927 patients with KDIGO stage 2 AKI were recruited into this international study. RRT was commenced either early (within 12 hours of randomisation), or delayed until either the occurrence of life-threatening complications of AKI or AKI persisting for >72 hours after randomization. 90-day mortality was similar in both arms of the study (43.9% vs 43.7%) and 38.2% of the delayed cohort avoided RRT. Interestingly, complications were higher in those undergoing early RRT (23.0% vs 16.5), as was continued need for RRT at 90 days (10.4% vs 6%)[3].

It can be surmised that in the absence of life-threatening complications of AKI, delay in initiation of RRT is not harmful, and may even prevent complications related to RRT. Furthermore, many patients who have delayed initiation may have spontaneous recovery of renal function and may not ever require RRT. AKIKI-2 has attempted to investigate whether delaying initiation of RRT even further, beyond the delayed strategy of previously published studies, can continue to provide additional benefits, and is the first trial to broach this subject. Whilst the primary analysis showed no difference in the primary outcome of RRT-free days between groups, a multivariate analysis showed a more-delayed strategy to be independently associated with a higher 60-day mortality risk. The cause of this additional mortality risk seen in this trial is as yet unclear.

AKIKI 2 confirms our lack of understanding of which patients with severe AKI need RRT. It is clear that a blanket approach of delaying RRT for as long as possible is not effective. Rather, AKIKI 2 highlights the need for us to predict AKI trajectories more accurately to help guide treatment decisions.[15] Given the heterogeneity within the pathophysiological processes of AKI, dynamic tests of kidney function or biomarkers which predict the persistence of AKI Stage 3 or the need for subsequent RRT will help to individualise patient management.[16,17] Finally, AKIKI 2 does provide further evidence that in patient with AKI stage 3, with prolonged oliguria and a serum urea <40 mmol/L, it is safe to postpone RRT for a limited period of time to allow for spontaneous resolution.

In patients with acute kidney injury, should we delay initiating renal replacement therapy as late as possible?

Probably not. Although no benefit was seen with further delaying renal replacement therapy beyond current standard practice, a very delayed strategy may be harmful.

References

1. Hoste EA, Bagshaw SM, Bellomo R, Cely CM, Colman R, Cruz DN, et al. Epidemiology of acute kidney injury in critically ill patients: the multinational AKI- EPI study. Intensive Care Med 2015 41;8:1411-1423

2. Bouchard J, Mehta RL. Timing of Kidney Support Therapy in Acute Kidney Injury: What Are We Waiting For? Am J Kid Dis 2022;79(3):417–426

3. STARRT-AKI Investigators, Canadian Critical Care Trials Group, Australian and New Zealand Intensive Care Society Clinical Trials Group, et al. Timing of initiation of renal-replacement therapy in acute kidney injury. N Engl J Med 2020;383(3):240-251

4. Gaudry S, Hajage D, Schortgen F, et al. Initiation strategies for renal-replacement therapy in the intensive care unit. N Engl J Med 2016 375;2,122-133

5. Barbar SD, Clere-Jehl R, Bourredjem A, et al. Timing of renal-replacement therapy in patients with acute kidney injury and sepsis. N Engl J Med. 2018 379;(15):1431-1442

6. Gaudry S, Hajage D, Martin-Lefevre L, Lebbah S, Louis G, Moschietto S et al. Comparison of two delayed strategies for renal replacement therapy initiation for severe acute kidney injury (AKIKI 2): a multicentre, open-label, randomised, controlled trial. Lancet 2021;397 (10281): 1293-1300

7. Coca, SG, Singanamala, S. and Parikh, C. Chronic kidney disease after acute kidney injury: a systematic review and meta-analysis. Kid Int 2012; 81(5):442–448

8. Zarbock A, Kellum JA, Schmidt C, et al. Effect of early vs delayed initiation of renal replacement therapy on mortality in critically ill patients with acute kidney injury: the ELAIN Randomized Clinical Trial. JAMA 2016;315(20):2190-2199

9. Vinsonneau C, Camus C, Combes A, de Beauregard MAC, Klouche K, Boulain T et al. Continuous venovenous haemodiafiltration versus intermittent haemodialysis for acute renal failure in patients with multiple-organ dysfunction syndrome: a multi-centre randomised trial. Lancet 2006;368:379–385

10. Lins RL, Elseviers MM, Van der Niepen P, Hoste E, Malbrain ML, Damas P et al. Intermittent versus continuous renal replacement therapy for acute kidney injury patients admitted to the intensive care unit: results of a randomised clinical trial. Nephrol Dial Transplant 2009;24:512–518

11. Schefold JC, Haehling S von, Pschowski R, Bender TO, Berkmann C, Briegel S, et al. The effect of continuous versus intermittent renal replacement therapy on the

outcome of critically ill patients with acute renal failure (CONVINT): a prospective randomised controlled trial. Crit Care 2014;18(1):R11

12. Ostermann M, Lumlertgul N. Wait and see for acute dialysis: but for how long? Lancet 2021;397(10281):1241–1243

13. Bouman CSC, Oudemans-van Straaten HM, Tijssen JGP, Zandstra DF, Kesecioglu J. Effects of early high-volume continuous venovenous hemofiltration on survival and recovery of renal function in intensive care patients with acute renal failure: A prospective, randomized trial. Crit Care Med 2002;30(10), 2205–2211

14. Zarbock A, Kellum JA, Schmidt C, Van Aken H, Wempe C, Pavenstädt H et al. Effect of Early vs Delayed Initiation of Renal Replacement Therapy on Mortality in Critically Ill Patients With Acute Kidney Injury. The ELAIN randomised Clinical Trial. JAMA 2016;315(20):2190-2199

15. Ostermann M, Bellomo R, Burdmann EA, et al. Controversies in acute kidney injury: conclusions from a Kidney Disease: Improving Global Outcomes (KDIGO) Conference. Kidney Int 2020;98:294-309

16. Hoste E, Bihorac A, Al-Khafaji A, et al. Identification and validation of biomarkers of persistent acute kidney injury: the RUBY study. Intensive Care Med 2020;46:943-953

17. Rewa OG, Bagshaw SM, Wang X, et al. The furosemide stress test for prediction of worsening acute kidney injury in critically ill patients: a multicenter, prospective, observational study. J Crit Care 2019;52:109-114

REVERSE-AKI

Vaara ST, Ostermann M, Bitker L, Schneider A, Poli E, Hoste E, et al. Restrictive fluid management versus usual care in acute kidney injury (REVERSE-AKI): a pilot randomised controlled feasibility trial. Intensive Care Med 2021;47:665–673

Introduction

Acute kidney injury (AKI) affects 30-60% of critically ill patients.[1] Development of an AKI in the critically ill patient is associated with an in-hospital mortality as high as 60%.[2] Development of an AKI also has significant resource implications, costing the UK National Health Service up to £620 million annually.[3]

Current management of AKI involves the administration of intravenous fluids to optimise the circulating intra-vascular volume, increase cardiac output and enhance renal perfusion pressure. Intravenous fluid therapy has been a traditional hallmark of AKI prevention and treatment.[4] However, given that autoregulation and excretion are often impaired in AKI, this patient cohort is particularly vulnerable to developing fluid overload with ensuing complications. A fluid overloaded state is associated with increased patient mortality. A prospective multi-centre observational study by Bouchard and colleagues demonstrated that in critically ill patients with an AKI, fluid overload, defined by a 10% increase in body weight relative to baseline, was independently associated with mortality, with an odds ratio for death, and adjusted for severity of illness, of 2.07 (95% CI, 1.27 to 3.37).[5]

It is hypothesised that fluid overload, driven in part by excessive administration of intravenous fluid, leads to elevated venous pressure which is transmitted to the capillary circulation. The resulting increase in hydrostatic pressure culminates in extravasation of fluid and oedema formation. The association between elevated venous pressure, renal venous congestion and development of AKI has been previously noted in critically ill patients.[6] Oedema reduces the functional capillary density and results in an increased diffusion distance between capillaries and cells, thus impairing oxygen delivery and leading to tissue ischaemia and organ failure.[7] A restrictive fluid management approach in adequately resuscitated patients may reduce venous congestion and improve kidney and other organ function.

There are no randomised control trials available on the role of different fluid management strategies specifically in critically ill patients with AKI.

Synopsis

Vaara et al. conducted a pilot feasibility trial comparing a restrictive fluid management (RFM) regimen to usual care among ICU patients with AKI to study the feasibility of this intervention in terms of separation in fluid balance, safety and protocol compliance. REVERSE-AKI trial tested the hypothesis that the RFM regimen would lead to a lower cumulative fluid balance at 72 hours post-randomization.

The REVERSE-AKI trial was an investigator-initiated, international, multi-centre, randomised, pilot feasibility study. The trial was conducted in five European and two Australian ICUs. Participants were randomised to either RFM or usual care using an electronic platform with an allocation ratio of 1:1.

Eligible patients were adults admitted to the intensive care unit with an AKI, who were between 12 and 72 hours from ICU admission, were deemed likely to remain in critical care for 48 hours following randomisation, and judged not be hypovolaemic. Patients were excluded if they were determined to be hypovolaemic, maintenance fluid therapy was deemed necessary or if there was ongoing active bleeding requiring transfusion. Additional reasons for exclusion were a lack of available baseline creatinine, a suspicion of parenchymal AKI, chronic RRT use, a requirement for RRT due to toxin ingestion, if RRT initiation was imminently expected, and significant dysnatraemias (Na^+ < 125 mmol/L or Na^+ > 155 mmol/L). The need for extracorporeal membrane oxygenation or molecular absorbent recirculating system was an exclusion criterion. Finally, those unable to consent, enrolled in other trials, pregnant or breast-feeding patients and those not for full active treatment were excluded.

The severity of AKI was graded using the Kidney Diseases: Improving Global Outcomes (KDIGO) criteria. The KDIGO criteria and presence of clinical signs of fluid accumulation served as stratification variables. Clinical signs of fluid accumulation were defined as peripheral pitting oedema and/or positive fluid balance with PaO_2/FiO_2 ratio less than 200 mm Hg.

Patients were randomly allocated to groups via a central electronic platform, in a 1:1 ratio, stratified by the severity of AKI, signs of fluid accumulation, and positive fluid balance, with a PaO_2/FiO_2 ratio < 200 mm Hg. Block allocation of varying size was employed. Due to the nature of the RFM intervention, only the statistician conducting the data analysis remained blinded to the treatment allocation.

The trial intervention, RFM, consisted of a bundle of treatment recommendations with an overall goal to achieve negative fluid balance. These recommendations included restricting total daily fluid input to medications, nutritional fluids and blood products.

Maintenance fluid administration was only permitted if enteral and parenteral nutrition was not feasible. However, fluid bolus therapy could be given if clinically deemed necessary. Importantly, the use of diuretics was encouraged to match fluid output to fluid input and generate a negative cumulative balance. If the fluid balance target could not be achieved with diuretic therapy, then consideration of renal replacement therapy (RRT) to remove fluid was encouraged. Fluid balance was calculated by subtracting total fluid output (urine output, losses to drains, losses from gastrointestinal tract, ultrafiltration by RRT) from total fluid input (intravenous and oral). Insensible losses were not considered. The intervention period was 7 days from randomisation or until ICU discharge, whichever occurred first. In the usual care group, fluid management was at the discretion of the treating clinical team.

Using unpublished data from the FINNAKI study, Vaara and colleagues estimated that the median cumulative fluid balance at 72 hours would be 2700 mL in the usual care group and 1500 mL in the RFM group (both with a SD of 2000 mL).[8] Thus, it was calculated that 50 patients in each arm would provide >80% power to detect a difference of 1200 mL in the primary outcome between treatment arms with a two-sided alpha of 0.05.

The primary outcome was cumulative fluid balance at 72 hours after randomisation, with adjustment for stratification variables of AKI severity and the presence of clinical signs of fluid accumulation. Secondary outcomes included: duration of AKI in days, defined by the KDIGO creatinine and urine output criteria; number of patients requiring RRT; cumulative fluid balance at 24 hours after randomization and at ICU discharge; cumulative dose of diuretics during the intervention period. Exploratory outcomes included days free of mechanical ventilation and alive at 14 days; days free of vasopressors and alive at 14 days; days free of ICU and alive at 14 days; days free of RRT and alive at 90 days; day 90 dialysis dependence; and day 90 mortality.

The primary analysis was performed on the intention-to-treat population, defined as all randomised subjects with consent to use data in the analysis. An additional sensitivity analysis was conducted in the per-protocol population, defined as the intention-to-treat population after exclusion of subjects who experienced protocol violation(s) or stayed in the ICU for less than 48 hours post-randomization. The primary, secondary and exploratory outcomes were adjusted for the stratification variables using two-tailed logistic regression (dichotomous outcomes) or a linear model (continuous outcome variables).

997 patients were screened, of whom 102 patients were randomised between October 2017 and January 2020 in seven ICUs across Europe and Australia. 100 patients were included in the analysis, 49 patients in the RFM group and 51 in the usual care group.

Baseline characteristics were reasonably well balanced between groups. The RFM group consisted of an older patient cohort (median age 71 years vs 64.5 years in the usual care group). Other comorbidities, including diabetes (50% of the RFM group vs 66% of the usual care group), hypertension (54.2% vs 65.3%), coronary artery disease (18.8% vs 31.4%) and COPD (16.7% vs 27.5%), were all more common in the usual care group. The most common reasons for ICU admission were cardiac arrest (8.2%), septic shock (7.2%) and gastrointestinal perforation/rupture (7.2%). The aetiology of AKI was multifactorial in 55% patients, with sepsis the predominant suspected aetiology in each group with 45.7% in the RFM group and 45.1% in the usual care group.

The primary outcome, cumulative fluid balance at 72 hrs, was significantly lower in the RFM group, with a mean difference of -1148 mls (95% CI, -2200 mls to -96 mL; P=0.033). Patients in the RFM group had lower cumulative fluid balance at 24 hours with a mean difference of -822 mls (95% CI, -1381 mL to -264 mL; P=0.004). Patients in the RFM group also had a lower cumulative fluid balance at ICU discharge or on day 7 with a mean difference of -1532 mL (95% CI, -3036 mL to -29 mL; P=0.046).

There was no significant difference between groups in AKI duration, with a median of 2 days in the RFM group and 3 days in the usual care group (P=0.071). Numerically, fewer patients in the RFM group required RRT than the usual care group (13% vs 30%; RR, 0.42; 95% CI, 0.16 to 0.91, P= 0.043). The median number of days alive and free of mechanical ventilation (13 vs 11.5; P=0.284), days alive and free of vasopressors (12 vs 11.5; P = 0.072), and days alive and free of RRT at 90 days (90 vs 90; P = 0.145) were also similar. Mortality at day 90 was 19.6% in the RFM group and 26.5% in the usual care group (P = 0.387).

More patients in the usual care group experienced at least one adverse event (11 vs 25; 22.4% vs 49%; risk ratio 0.46; 95% CI, 0.36 to 0.63, P=0.001). Serious adverse events were observed in 6 (12.2%) patients randomised to RFM group and in 16 patients (31.4%) randomised to the usual care group (RR, 0.39; 95% CI, 0.15 to 0.86, P=0.031). The most common adverse incidents in both groups were related to electrolyte disturbances.

Critique

This is the first randomised controlled trial to compare a RFM approach with usual care in critically unwell patients with an AKI. This study begins to address an important clinical question and the results obtained in REVERSE-AKI will inform the design of

future studies. The trial design is robust and the trial protocol and statistical analysis plan were published prior to completion of data collection.[9] The multi-centre approach is important as this captures the wide range of fluid treatment practices between intensive care units. In addition, the trial outcomes were appropriately targeted with a particular focus on the safety of restrictive fluid therapy. The use of a bundle of recommendations to implement a restrictive fluid management approach provided autonomy to the clinical team and presented a platform to enable tailored treatment to individual patients. AKI was defined and graded as per the KDIGO criteria. The use of a consensus definition of AKI permits the comparison of this study with other research in the field.

Due to the nature of the intervention it was not feasible to blind clinicians. Additionally, the use of recommendations as an intervention permits potential inconsistency in the intervention being tested. There exists an important trade-off between allowing tailoring of patient management and clinician autonomy versus losing intervention compliance. Although statistical significance was reached, a between-group difference in fluid balance of just over 1 litre in 72 hours may not be clinically important. Moreover, calculation of fluid balance is notoriously inaccurate, and this study was unable to account for insensible losses. Therefore, the true fluid balance of patients in both groups may differ from that reported.

A key exclusion criterion was being intra-vascularly hypovolemic. This is a subjective judgement which introduces selection bias. An attempt to define intra-vascular hypovolaemia in terms of haemodynamic variables may have ensured a more objective screening process. The proportion of patients screened who were subsequently enrolled was low, with a quarter excluded due to a clinical impression of hypovolaemia, despite having been in the intensive care unit for at least 12 hours. In the ANDROMEDA-SHOCK study, albeit in a population with septic shock, a very low proportion of patients were fluid responsive at this stage.[10] It is highly likely this reflects a preconception among clinicians that many patients are hypovolaemic, despite little supporting evidence. Furthermore, the large cohort of patients screened but excluded due to perceived hypovolaemia represent an important patient cohort that must be considered in future research. The adjustment of future study protocols to permit the correction of perceived hypovolaemia could enhance patient enrolment and is worthy of consideration. This study had a relatively slow recruitment rate with a median recruitment of 0.8 patients/centre/month. Including those patients suspected of being hypovolaemic, but who lack clear evidence to support this, may have improved this.

The trialists do not provide information on the type of fluids administered. This is relevant as the type of fluid used may have impacted the anticipation of possible kidney

injury, given the widespread perception of chloride induced kidney injury. As a clinician open-label trial, this knowledge may have influenced other management decisions. Ironically, with the recent publication of the BaSICS[11] and PLUS[12] randomised control trials, comparing Plasma-Lyte 148 with 0.9% saline, and a systematic review and meta analysis[13] comparing balanced crystalloids, this fear is probably unfounded at low levels of crystalloid administration.

At 72 hours following randomisation, only 66 patients remained in ICU. 29 had been discharged, 4 were deceased and 1 had withdrawn consent for further data collection. These 34 patients were included in the analysis despite their relatively short ICU admission which may limit the generalisability of the study results.

Protocol violations occurred in 36.7% of the RFM group compared to 9.8% in the usual care arm. In the RFM group, use of excess maintenance fluid in 18.4% of patients was the most common protocol violation. While this may reflect individual local practice, such divergence needs to be addressed in future trial protocols. This study defined and graded AKI using the widely adopted KDIGO criteria. Serum creatinine and urine output are key to the KDIGO system. However, serum creatinine may be influenced by non-renal and non-GFR related factors which limits its use as surrogate markers of GFR.[14]

The REVERSE-AKI trial provides further evidence that in intensive care patients with an AKI, who are not considered to be hypovolemic, using a combined strategy targeting control of daily fluid balance is feasible, safe and provides strong rationale to proceed to a larger phase III study which may influence practice. Ultimately, this study is reassuring and encouraging as to the safety of a RFM approach in critically ill patients with AKI.

Where this sits in the body of evidence

No randomised controlled trial has previously studied a RFM regimen specifically in critically ill patients with AKI. However, the association between both the volume of fluid administered and accumulation of a positive fluid balance with adverse outcomes is well recognised. Payen and colleagues conducted a sub analysis of the SOAP study.[15] This was a prospective multi-centre observational study designed to evaluate the epidemiology of sepsis in European countries. Of the 3147 patients enrolled in the SOAP study, 1120 (36%) developed AKI. Patients with AKI had higher mortality rates than patients without AKI (60-day mortality, 35.7% vs 16.4%; $P < 0.01$). This study identified mean fluid balance as an independent risk factor for 60-day mortality in critically ill patients with an AKI .

The Fluid and Catheter Treatment Trial (FACTT)[16] was a randomised study which compared conservative fluid therapy to liberal fluid therapy in 1000 patients with ARDS.

The mean (±SE) cumulative balance during the first seven days was −136 ± 491 mL in the conservative-strategy group and 6992 ± 502 mL in the liberal-strategy group (p<0.001). Although there was no statistically significant difference in the percentage of patients receiving RRT between groups, there was a trend towards less RRT in the conservative fluid therapy group (10% in the conservative-strategy group vs. 14% in the liberal-strategy group, P = 0.06).

A post-hoc analysis[17] of FACTT was conducted by Liu and colleagues in which they investigated the incidence of AKI between the conservative fluid therapy and liberal fluid therapy arms following an adjustment for fluid balance. This is relevant as the accumulation of fluid has a dilutionary effect on creatinine which may mask the development of an AKI. Following adjustment for fluid balance, the incidence of AKI was higher in those managed with the liberal fluid protocol (66% vs 58%, P= 0.007).

The CLASSIC pilot trial[18] compared a protocol of restricted fluid resuscitation with standard care in 151 patients with septic shock and who had received initial fluid resuscitation. The co-primary outcome measures were the amount of resuscitation fluid in the first 5 days after randomisation [mean difference −1.2 L; 95 % CI, −2.0 to −0.4; P < 0.001) and the amount of resuscitation fluid given after randomisation during the entire ICU stay (mean difference, −1.4 L; 95% CI, −2.4 to −0.4; P < 0.001). This study demonstrated a lower number of patients with deterioration of their AKI in the fluid restriction group compared with the standard care group (37% vs 54%; OR, 0.46; 95% CI, 0.23 to 0.92; P=0.03).

The RADAR-2 study[19] investigated the feasibility of a randomised trial comparing conservative fluid administration and deresuscitation with usual care. 89 patients were assigned to the intervention arm and 90 patients were assigned to the usual care group. The primary endpoint was fluid balance in the 24 hours up to the start of study day 3. The mean (SD) 24-hour fluid balance up to study day 3 was lower in the intervention group (difference, – 840 ± 1746 mL) than the usual care group. In this study there was no difference in the incidence of new or worsening AKI (intervention 15.7% vs usual care 13.3%; P=0.65).

In the perioperative setting the RELIEF trial[20] compared a restrictive fluid regimen to a liberal fluid regimen in 3000 patients undergoing major abdominal surgery. Here the protocol dictated that fluid be withheld in the restrictive arm even when marked oliguria was present. During and up to 24 hours after surgery, 1490 patients in the restrictive fluid group had a median (IQR) intravenous-fluid intake of 3.7 litres (2.9 to 4.9), as compared with 6.1 litres (5.0 to 7.4) in 1493 patients in the liberal fluid group (P<0.001). The rate of AKI was 8.6% in the restrictive fluid group and 5.0% in the liberal fluid group.

In conclusion, REVERSE-AKI adds to the weight of data which suggests that a RFM approach is safe among critically unwell patients with an AKI. Furthermore, there is a signal of efficacy in the RFM arm which supports the need to conduct larger trials investigating this strategy.

Should we implement a restrictive fluid regime in critically ill patients?

Not on the basis of REVERSE-AKI, which was a pilot trial testing feasibility. Larger trials powered for clinically relevant endpoints will be needed to change clinical practice.

References

1. Hoste EA, Kellum JA, Selby NM, et al. Global epidemiology and outcomes of acute kidney injury. Nat Rev Nephrol 2018;14(10):607–25.

2. Uchino S, Kellum JA, Bellomo R, et al. Acute renal failure in critically ill patients: a multinational, multicenter study. JAMA J Am Med Assoc 2005;294(7):813–8.

3. National Institute for Health and Care Excellence. Acute kidney injury: prevention, detection and management. 2019;Available from: Available online from: https://www.nice.org.uk/guidance/ng148/resources/acute-kidney-injury-prevention-detection-and-management-pdf-66141786535621

4. Ostermann M, Liu K, Kashani K. Fluid management in acute kidney injury. Chest 2019;156(3):594–603.

5. Bouchard J, Soroko SB, Chertow GM, et al. Fluid accumulation, survival and recovery of kidney function in critically ill patients with acute kidney injury. Kidney Int 2009;76(4):422–7.

6. Legrand M, Dupuis C, Simon C, et al. Association between systemic hemodynamics and septic acute kidney injury in critically ill patients: a retrospective observational study. Crit Care 2013;17(6):1–8.

7. Ince C. Hemodynamic coherence and the rationale for monitoring the microcirculation. Crit Care 2015;19(3):1–13.

8. Nisula S, Kaukonen K-M, Vaara ST, et al. Incidence, risk factors and 90-day mortality of patients with acute kidney injury in Finnish intensive care units: the FINNAKI study. Intensive Care Med 2013;39(3):420–8.

9. Vaara ST, Ostermann M, Selander T, et al. Protocol and statistical analysis plan for the REstricted fluid therapy VERsus Standard trEatment in Acute Kidney Injury—REVERSE-AKI randomised controlled pilot trial. Acta Anaesthesiol Scand 2020;64(6):831–8.

10. Hernández G, Ospina-Tascón GA, Damiani LP, et al. Effect of a resuscitation strategy targeting peripheral perfusion status vs serum lactate levels on 28-day mortality among patients with septic shock: the ANDROMEDA-SHOCK randomised clinical trial. JAMA J Am Med Assoc 2019;321(7):654–64.

11. Zampieri FG, Machado FR, Biondi RS, et al. Effect of intravenous fluid treatment with a balanced solution vs 0.9% saline solution on mortality in critically ill patients: the BaSICS randomised clinical trial. JAMA 2021;326(9):818–29.

12. Finfer S, Micallef S, Hammond N, et al. Balanced Multielectrolyte Solution versus Saline in Critically Ill Adults. N. Engl. J. Med. 2022;386(9):815–26.

13. Hammond NE, Zampieri FG, Di TGL, et al. Balanced Crystalloids versus Saline in Critically Ill Adults — A Systematic Review with Meta-Analysis. NEJM Evid 2022;1(2):EVIDoa2100010.

14. Schetz M, Schortgen F. Ten shortcomings of the current definition of AKI. Intensive Care Med 2017;43(6):911–3.

15. Payen D, de Pont A, Sakr Y, et al. A positive fluid balance is associated with a worse outcome in patients with acute renal failure. Crit Care 2008;12(3):R74.

16. Wiedemann HP, Wheeler AP, Bernard GR. Comparison of two fluid-management strategies in acute lung injury. J Vasc Surg 2006;44(4):909.

17. Liu KD, Thompson BT, Ancukiewicz M, et al. Acute kidney injury in patients with acute lung injury: impact of fluid accumulation on classification of acute kidney injury and associated outcomes. Crit Care Med 2011;39(12):2665.

18. Hjortrup PB, Haase N, Bundgaard H, et al. Restricting volumes of resuscitation fluid in adults with septic shock after initial management: the CLASSIC randomised, parallel-group, multicentre feasibility trial. Intensive Care Med 2016;42(11):1695–705.

19. Silversides JA, McMullan R, Emerson LM, et al. Feasibility of conservative fluid administration and deresuscitation compared with usual care in critical illness: the Role of Active Deresuscitation After Resuscitation-2 (RADAR-2) randomised clinical trial. Intensive Care Med 2022;48(2):190–200.

20. Myles PS, Bellomo R, Corcoran T, et al. Restrictive versus liberal fluid therapy for major abdominal surgery. N Engl J Med 2018;378(24):2263–74.

Endocrine Trials

CONTROLING

Bohé J, Abidi H, Brunot V, Klich A, Klouche , Sedillot N et al. Individualised versus conventional glucose control in critically-ill patients The CONTROLING Study. A randomized clinical trial. Intensive Care Med. 2021;47:1271-83

Introduction

Hyperglycaemia is common in critically ill patients due to stress induced hormonal adaption and is associated with adverse outcomes[1]. Strict glycaemic control in diabetes mellitus reduces complications[2] and critical care management has mirrored this principle that tighter control should equate to better outcomes.

This hypothesis was initially supported by the results of a single centre trial from a Belgium surgical ICU.[3] A strict glycaemic range of 4.4 – 6.1 mmol/L (80 – 110 mg/dL) was compared with a more liberal approach, using insulin only if the blood glucose rose above 12 mmol/L (215 mg/dL) and then maintaining it between 10 – 11.1 mmol/L (180 – 200 mg/dL). ICU mortality was significantly lower in the restrictive group (8% vs 4.6%), as were the prevalence of bloodstream infections, ICU-acquired weakness and requirement for renal replacement therapy. Although less definitive, clinical benefits were also confirmed in critically ill medical patients[4]. However, the reproducibility of these results has been questioned, with particular focus on the increased risk of hypoglycaemic events[5]. Subsequently, the larger multi-centre NICE SUGAR trial reported that intensive glucose control (4.4 – 6.1 mmol/L), in comparison to a more liberal approach (<10 mmol/L), was associated with increased mortality.[6]

A further consideration is the complicating factor of pre-existing known or undiagnosed diabetes. These patients are more likely to have higher chronic pre-admission blood glucose measurements. The NICE SUGAR trial analysed outcomes of known diabetic patients and confirmed similar harmful results to the general trial population. An even more liberal approach to glycaemic control, in comparison to non-diabetic patients, has been suggested to be safer.[6,7] More liberal control of blood sugars conflicts with optimal diabetes care[2] however, and chronic hyperglycaemia may modulate glucose transporters and render diabetic patients more susceptible to even mild hypoglycaemia.[8] In this setting the CONTROLING study was designed to compare standard glycaemic control against individualised glycaemic control using the HbA1c as a measure of the patients usual blood sugar levels.

Synopsis

This multi-centre, double-blind, parallel group, randomised controlled trial performed in 12 ICUs in France investigated the effect of individualized glycaemic control based on a

HbA1C level versus a standard regime of less than 10 mmol/L (180 mg/dL). Adult patients admitted to ICU who were not expected to be discharged within 48 hours and were unable to tolerate an oral diet were eligible for randomisation. Patients were excluded if they had received more than three blood transfusions in the previous three months, had limitations of therapy or were pregnant.

Prior to randomisation all patients had a HbA1C performed and were assigned a glycaemic target of less than 180 mg/dL. Glycaemic control was managed using a web based application, which incorporated multiple insulin sliding scales with protocol based rules to select an appropriate sliding scale. The intervention group had a 'usual' glycaemia calculated using the formula: 28.7×HbA1C-46.7 (in mg/dL, with HbA1C in %). Glycaemic control was then targeted to usual glycaemia + 15 mg/dL with a maximum target of 217 mg/dL (12.1 mmol/L) and a minimum of 111 mg/dL (6.2 mmol/L). The control group remained with a glycaemic target of less than 180 mg/dL (10.0 mmol/L). Glycaemic control was managed by the bedside nurse and continued until ICU discharge. Treating clinicians were blinded to the glycaemic strategy but all other management decisions were left to the clinical team.

The primary outcome measure was 90-day all-cause mortality after randomisation. Secondary endpoints included 28-day mortality, length of ICU stay, duration of ventilation, renal replacement therapy and anti-microbial requirements. Complications related to glycaemic control were recorded for severe hypoglycaemia (below 40 mg/dL / 2.2 mmol/L) which was considered a serious adverse event and moderate hypoglycaemia (40 - 71 mg/dL / 2.2 – 3.9 mmol/L).

Assuming an estimated 90-day mortality of 22%, a total sample size of 4200 patients was calculated to give a 90% power to detect an absolute difference in mortality of 4% in favour of the conventional control group using the Chi-squired test with a two-sided significance of 5%. The 90-day survival curves were estimated using the Kaplan–Meier method and compared using the Log-rank test. Hazard ratios were estimated using a Cox proportional hazards model adjusted by age, sex, body mass index, Charlson score, diabetes status, ICU admission type, SAPS II score and invasive ventilation. Glycaemic control was reported as time weighted average glycaemia and reported according to different HbA1C strata. The time spent in different glycaemic ranges were also recorded. Four interim analyses were planned.

Over a 14-month period, 5326 patients were admitted to the participating ICUs. Almost 700 patients were excluded as they were not expected to stay for more than 48 hours, 827 patients did not have an HbA1c within 96 hours and 1300 patients were not assessed. 423 patient met other exclusion criteria. 2075 patients were randomised, of

which 158 did not received the intervention. A total of 1917 patients were included; 942 allocated to the HbA1c targeted group and 975 to the conventional control group. Baseline characteristics were similar in the two groups; 53% of patients were mechanically ventilated and 31% required vasopressor support. The median SAPS II score was 46 (35-62) vs 48 (37-62) in the HbA1c targeted and conventional groups, respectively. Around one third of patients were considered to be diabetic of which 25% were on insulin prior to admission and a 25% were undiagnosed (HbA1c > 6.5%).

Patients were randomised a median of 1.2 days after ICU admission and spent approximately a further 4 days on the assigned treatment algorithm. Significantly more patients required insulin in the intervention group (702 vs 486, P<0.0001). During the intervention the time-weighted average glycaemia was significantly different between the two groups. Values were significantly lower in the intervention group for the HbA1c strata below 7%, and higher for the strata above 8%. The HbA1c strata 7-8% had similar glycaemic targets and therefore there was no difference in the time weighted average glycaemia results. The percentage of time spent between the glycaemic target – 36 mg/dL and the glycaemic target was significantly different (51% (35-69) vs 25% (7-42) p<0.0001) for the two groups.

The trial was stopped early after an interim analysis due to the low likelihood of benefit and possibility of harm related to hypoglycaemia. There was no significant difference in the primary outcome of 90-day mortality; 32.8% vs 30.5% in the intervention and control groups, respectively (HR, 1.1; 95% CI, 0.97 to 1.36; P=0.1).

There were no significant differences in the secondary outcomes, including survival at 28-days (74.3%, vs 78%, P=0.07), ICU length of stay (4.10 vs 4.32 days, P=0.23) and in use of intensive care resources. There was also no significant difference in the frequency of severe hypoglycaemia between the two groups (3.9% vs. 2.5%; P=0.09), however, hypoglycaemia below 72 mg/dL (4.0 mmol/L) was significantly more frequent in the intervention group (31.2% vs 15.8%; P<0.0001). A post hoc analysis suggested a significantly higher risk of mortality at 90 days in the intervention group for non-diabetic patients (HR 1.3, 95% CI, 1.05 to 1.59; P=0.018).

Critique

Glycaemic control has been an important, and at times controversial, aspect of the management of critical care patients. The enthusiasm for the once lauded intensive glucose control protocols, which showed benefits in terms of both mortality and morbidity,[3,4] has been largely dispelled by the opposing results of the larger multi centre NICE SUGAR trial.[6] Explanations in terms of the differences in blood glucose targets, accuracy of monitoring and feeding strategies have been postulated to reconcile these

opposing results.[7] The potential that the effect of intensive glucose control might vary in different patient populations may also influence trial results. Diabetic patients did not derive benefit in a combined analysis of the Leuven studies,[9] while the association between blood glucose concentrations and mortality suggests a more liberal approach to glycaemic control may be more appropriate, particularly in poorly controlled diabetes.[7]

Critical care trial conclusions often propose individualised therapy. In diabetes, HbA1c correlates with glucose control over the life of the red blood cell and management based on reduction in HbA1c levels improves outcomes.[2] In critical illness, higher HbA1c levels indicating poorer glycaemic control has been associated with increased glucose variability and hypoglycaemia, and seems to affect the relationship between ICU glycaemic control and mortality.[10] Personalised glucose management based on preadmission glycaemic control therefore has a sound physiological basis and yet the CONTROLING Trial ultimately failed to show that a strategy based on HbA1c improved outcomes.

The results once again confirmed the dangers of not only severe, but also mild hypoglycaemia, in the general ICU population. However, although the use of HbA1c is physiologically logical, and arguably useful as almost 9% of patients previously unknown to be diabetic, met diagnostic criteria for diabetes, this may have inadvertently been problematic. The HbA1c test was performed in accredited laboratories but delays in processing and time to recruit patients ultimately exposed patients in the intervention group to a median of a day on the conventional glycaemic protocol. This may have diluted any derived benefit.

The distribution of HbA1c may have also reveal a potential difficulty with the trial. HbA1c ranged from 4% to almost 9% but the median values were within a normal range - 5.8% in both groups, with the majority of patients in the trial having normal values. As a potential benefit of targeted glycaemic control was to avoid relative hypoglycaemia in patients with chronic hyperglycaemia, a group previously identified as having potentially worse outcomes,[10] then recruitment of patients with predominantly normal HbA1c may have missed the target population. In addition, this implies patients with prior normal glycaemic control were exposed to tight glycaemic control (calculated glycaemia + 15 mg/dL), a regime that the NICE Sugar trial deemed harmful. A post hoc analysis confirmed the harmful effects of this glycaemic strategy. The relatively small proportion of patients with higher HbA1c levels had similar targets to the conventional control group and had comparable outcomes. It remains to be confirmed if the HbA1c is the best method for targeting personalised glycaemic control.

The CONTROLING trial also highlights the difficulties, or perhaps realities, of glycaemic management and research in critically ill patients. The trial used an algorithm developed by the trialists, which was unvalidated, but had been in routine use prior to study commensal. Despite minimal protocol deviations (less than 1%), the time in the individualized target range was just 51% [35–69%], reflecting the difficulties of managing truly tight glycaemic control. The incidence of hypoglycaemic events (23.4%) also emphasises the problem of managing these patients.

Finally, the CONTROLING study demonstrated only a small difference in time-weighted blood glucose measurements, partially due to lower than expected glucose measurements and a lack of insulin requirement in the control arm. The between group difference was just 13 mg/dL (0.7 mmol/L), which, in the context of this trial, although these were statistically significant differences in time weighted glucose measurements when stratified by HbA1c categories, the differences may not have been clinically relevant. These differences were less than previous trials and likely reflects an under powering of the trial to detect any outcome differences.

Post CONTROLING, some unanswered questions remain regarding glycaemic control. Hypoglycaemia is harmful, and at present a slightly more liberal approach to glycaemic control in the setting of stress induced hyperglycaemia is superior to more stringent glycaemic control, as the complication of hypoglycaemia currently seems very difficult to avoid. Whether even more liberal glycaemic control in previously poorly controlled or undiagnosed diabetes is beneficial requires further investigation. The very recently published LUCID[11] trial addressed this exact issue, comparing a liberal (10 – 14 mmol/L) with a conservative strategy (6.0 - 10 mmol/L) in type 2 diabetics in the ICU. Although there were less episodes of hypoglycaemia (5% vs 18%; incident rate ratio, 0.21; 95% CI, 0.09 to 0.49; P<0.001), mortality was numerically higher with the liberal approach (29.5% vs 24.9%; difference 4.6%; 95% CI, -3.9 to 13.2%; P=0.29).

Where this sits in the body of evidence

The original “Leuven” trial investigating an intensive insulin regime started the modern focus on tight glycaemic control. This single centre trial randomised 1548 ventilated patients admitted to a surgical intensive care to intensive glucose control (target 80 to 110 mg/dL / 4.4 to 6.1 mmol/L) or conventional control (target 180 – 200 mg/dL / 10.0 to 11.1 mmol/L). The primary outcome measure was death from any cause during the ICU stay. Hypoglycaemia (blood glucose less than 40 mg/dL / 2.2 mmol/L) occurred in 39 patients in the intensive-treatment group and in 6 patients in the conventional treatment group. Less patients in the intensive group had died prior to ICU discharge (4.6% vs 8.0%; P < 0.04 after adjustment). Benefit was attributable to patients who remained in the intensive care for more than 5 days, with the largest mortality reduction

in patients with multiple-organ failure with sepsis. Intensive insulin therapy also reduced in-hospital mortality by 34%, bloodstream infections by 46%, acute renal failure requiring dialysis or hemofiltration by 41% and critical-illness polyneuropathy by 44%. Patients receiving intensive therapy were less likely to require prolonged mechanical ventilation and intensive care.[3]

In a follow up to the first "Leuven" trial, which took place in a surgical ICU, the same trial team replicated the trial in their medical ICU. 1200 patients were randomised to intensive glucose control (target 80 mg to 110 mg/dL) or conventional control (target 180 – 215 mg/dL / 10 - 12). The primary outcome measure was in-hospital mortality. Despite significant difference in blood glucose control, there was no difference in hospital mortality (40.0% vs. 37.3% in the control vs intensive-treatment groups, respectively, P=0.33). However, among 433 patients who stayed in the ICU for less than three days, mortality was greater among those receiving intensive insulin therapy. In contrast, among the 767 patients admitted for three or more days, in-hospital mortality in the 386 who received intensive insulin therapy was reduced from 52.5% to 43.0% (P=0.009). Morbidity was lower in the intensive glucose control group due to reduced acute kidney injury, faster ventilator weaning and shorter length of stay.[4]

In a large multi-centre randomised control trial, 6104 patients within 24 hours of admission to intensive care were randomised to intensive glucose control (target 81 mg to 108 mg/dL / 4.5 – 6.0 mmol/L) or conventional control (target ≤ 180 mg/dL / 10 mmol/L). The primary outcome was death from any cause at 90 days. A total of 829 patients (27.5%) in the intensive-control group and 751 (24.9%) in the conventional control group died (odds ratio for intensive control, 1.14; 95% CI, 1.02 to 1.28; P=0.02). There were more episodes of severe hypoglycemia (blood glucose < 40 mg/dL / 2.2 mmol/L) in the intensive-control group (6.8% vs 0.5%; P<0.001). The study concluded that a higher glucose target reduced mortality in critically ill patients.[6]

Should we individualise glycaemic control of critically ill patients based on HbA1c measurements?

No, based on the CONTROLING trial, this approach does not appear beneficial and may be harmful.

References

1. Badawi O, Waite MD, Fuhrman SA & Zuckerman IH. Association between intensive care unit-acquired dysglycemia and in-hospital mortality. Crit Care Med 2012; 40:3180–88

2. Diabetes Control and Complications Trial Research Group, Nathan DM, Genuth S, Lachin J, Cleary P, Crofford O, Davis M, et al. The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. N Engl J Med 1993;329(14):977-86

3. Van den Berghe G, Wouters P, Weekers F, Verwaest C, Bruyninckx F, Schetz M, et al. Intensive insulin therapy in critically ill patients. N Engl J Med 2001;345(19):1359-67

4. Van den Berghe G, Wilmer A, Hermans G, Meersseman W, Wouters PJ, Milants I, et al. Intensive insulin therapy in the medical ICU. N Engl J Med 2006;354:449–61

5. Wiener RS, Wiener DC, Larson RJ. Benefits and risks of tight glucose control in critically ill adults: a meta-analysis. JAMA 2008;300(8):933-44

6. Finfer S, Chittock DR, Yu-Shuo S et al. NICE-SUGAR Study Investigators. Intensive versus Conventional Glucose Control in Critically Ill Patients. N Engl J Med 2009;360:1283-97

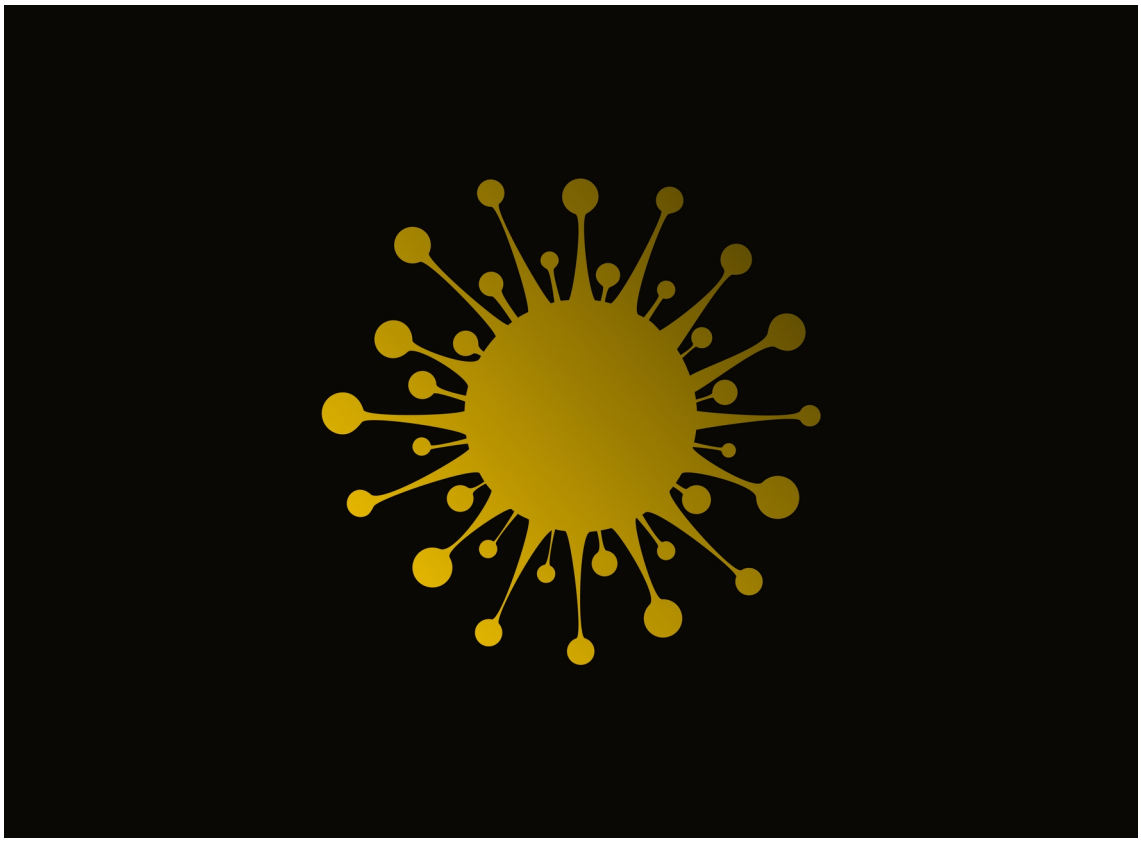
7. Gunst J, De Bruyn A & Van den Berghe G. Glucose control in the ICU. Curr Opin Anaesthesiol 2019;32:156–62

8. Kwan TN, Zwakman-Hessels L, Marhoon N, Robbins R, Mårtensson J, Ekinci E et al. Relative hypoglycemia in diabetic patients with critical illness. Critical care medicine 2020;48(3):e233-40

9. Van den Berghe G, Wilmer A, Milants I, Wouters PJ, Bouckaert B, Bruyninckx F et al. Intensive insulin therapy in mixed medical/surgical intensive care units: benefit versus harm. Diabetes 2006;55:3151–3159

10. Krinsley JS, Rule P, Pappy L, Ahmed A, Huley-Rodrigues C, Prevedello D, et al. The interaction of acute and chronic glycemia on the relationship of hyperglycemia, hypoglycemia, and glucose variability to mortality in the critically ill. Critical Care Medicine 2020;48(12):1744-51

11. Poole AP, Finnis ME, Anstey J, Bellomo R, Bihari S, Birardar V, et al. The Effect of a Liberal Approach to Glucose Control in Critically Ill Patients with Type 2 Diabetes: A multicenter, parallel-group, open-label, randomized clinical trial. Am J Respir Crit Care Med 2022;epublished May 20th



Sepsis Trials

VICTAS

Sevransky JE, Rothman RE, Hager DN, Bernard GR, Brown SM, Buchman TG, et al. Effect of Vitamin C, Thiamine, and Hydrocortisone on Ventilator- and Vasopressor-Free Days in Patients With Sepsis. The VICTAS Randomized Clinical Trial. JAMA 2021;325(8):742-750

Introduction

The momentum to investigate the combination of vitamin C, hydrocortisone and thiamine developed after the publication of a retrospective, single-centre, before-and-after case series by Paul Marik,[1] followed shortly after by a presentation of these data at the Critical Care Reviews Meeting 2017, and a subsequent campaign of promotion on social media and elsewhere.

Vitamin C is a co-factor for catecholamine synthesis and necessary to maintain circulatory performance.[2] It is also anti-inflammatory, limiting endothelial injury, and is immunomodulatory, promoting the antibacterial activity of a range of leukocyte subsets. Its levels drop during sepsis making it an inviting prospect to study. A side effect of high dose vitamin C is the generation of oxalate, which can crystallise in tissues. Patients with acute kidney injury are at risk of oxalate crystal deposition in the kidneys, an effect which can be ameliorated by the addition of thiamine, itself often deficient during episodes of sepsis. Thiamine acts as a cofactor to reduce the production of oxalate. Corticosteroids, via a myriad of effects, are anti-inflammatory, improve endothelial barrier function and restore vascular reactivity to catecholamines during sepsis.

With a plausible underlying biological effect of vitamin C in sepsis, and rationale for the addition of corticosteroids and thiamine, the combination appeared attractive to investigate further. As all three agents are easily available and cheap, over a dozen randomised controlled trials including 1 or all 3 of these elements were soon registered on the trials registry website clinicaltrials.gov. A long held lay belief that vitamin C can reduce or minimise infections, with the common cold often cited as an example, further builds the narrative that a cheap and easy therapy exists in clear reach – the “cure for sepsis”.

Synopsis

The VICTAS trial sought to determine if the combination of vitamin C, thiamine, and hydrocortisone was effective in patients with sepsis. This was an adaptive, multi-centre, placebo-controlled, randomised trial and ran at 43 American centres between 2018 and 2019.

Adult patients, either in the ICU, or in the emergency department with an anticipated ICU admission, with sepsis-induced respiratory and/or cardiovascular dysfunction, were eligible. Patients were considered to have sepsis if they had a blood culture taken and an antimicrobial agent administered. Sepsis-induced respiratory dysfunction was considered to be the presence of hypoxia, defined as either a $PaO_2/FiO_2 \leq 300$ mm Hg (26.6 kPa) or $SpO_2/FiO_2 \leq 315$, and the need for respiratory support, either invasive mechanical ventilation, non-invasive mechanical ventilation or high flow oxygen therapy with a $FiO_2 \geq 0.4$ or a flow rate ≥ 40 L/min. Circulatory dysfunction was defined by a requirement for a vasopressor for at least 1 hour to maintain a mean arterial pressure ≥ 65 mm Hg, after at least 1 L of intravenous fluid resuscitation. Exclusion criteria included age < 18 years, weight < 40 kg, no ongoing requirement for organ support at the time of randomisation, duration of respiratory or circulatory organ dysfunction ≥ 24 hours before randomisation, limitations of care, current hospitalisation duration of > 30 days, chronic need for circulatory or respiratory support, preceding use of vitamin C > 1 g/day within 24 hours, or allergy to any of the study agents.

Enrolment, randomisation and allocation to either the intervention or control groups occured via a central electronic system using statistical software. Patients were randomised in a 1:1 fashion in permuted blocks of 2, 4 or 6, stratified by site. Study drug kits were centrally prepared, identifiable by a study drug number only, and transferred to study sites. After randomisation, the local pharmacy prepared the individual study drugs based on the contents of the numbered study drug kit identified by the randomisation process. These ready-to-administer active compounds, or matching saline placebos, were delivered to the research team in a blinded fashion.

Once randomised, patients received the study drugs within 4 hours, and continued to receive them every 6 hours, up to 96 hours, death or discharge from the ICU. The intervention group received intravenously 1.5 g of vitamin C, 100 mg of thiamine hydrochloride, and 50 mg of hydrocortisone sodium succinate in a blinded fashion. The control group received matching placebo.

The primary outcome was ventilator- and vasopressor-free days (VVFDs) within the first 30 days. Although the trial was powered on the primary outcome, it also took into account the secondary outcome of mortality. An adaptive sample size calculation was used. The initial enrollment target was 500 patients, with interim analyses planned after the recruitment of 200, 300 and 400 patients. If no large effect was identified on mortality, the trial could continue to recruit up to 2000 patients to seek a smaller effect size on VVFDs. For the primary outcome, patients who died were assigned 0 VVFDs, while patients with missing data were assigned the last clinical state they were observed

with – if receiving ventilation when last seen, this was extrapolated to day 30 and the assumption made the patient has zero days free of vasopressors or ventilation. The trial design aimed to identify a difference in the primary outcome of 1.5 VVFDs, based on an expected mortality rate of 25%, whilst maintaining a 1-sided type I error rate at 2.5%.

The trial was stopped after the recruitment of 501 patients after a request for additional funding was declined by the funding body, the Marcus Foundation. No predefined stopping criteria were met.

3243 patients were screened, 2742 excluded and 501 enrolled. 252 patients were randomised to the intervention group and 249 to the control group. The most common reasons for exclusion were a non-septic indication for organ support (n=735), domiciliary oxygen use (n=514), patient refusal (n=406), limitations of care (n=346) and symptoms improving prior to enrolment (n=274). Groups had similar characteristics at baseline. The mean age was 62 years, 46% were female, and the median weight was 80 kg. Patients had a high severity of illness, with 38% receiving vasopressor support alone, 21% receiving mechanical ventilation alone and 41% both. The median APACHE II score was 27, SOFA score 9 and serum lactate 3 mmol/L. Median mean arterial pressure was 71 mm Hg, respiratory rate 22 breaths per minute, and heart rate in the mid 90s / minute. The median time to treatment was 14.7 hours. The lungs were the most common sources of infection, at approximately 38%, and both groups had similar types of pathogens. Near equal numbers of patients daily in both groups received open label corticosteroids of at least 200 mg of hydrocortisone or equivalent (32% and 33%, in the intervention and control groups, respectively).

The vast majority of doses of study medications were administered. Of the 501 patients, just 20 missed more than 1 dose of vitamin C or placebo, 6 missed more than 1 dose of thiamine or placebo, and 3 missed more than one dose of hydrocortisone or placebo.

There was no difference in the primary outcome of median (IQR) VVFDs; intervention group, 25 (0-29) vs control group, 26 (0-28) days; (difference, −1 day; 95% CI, −4 to 2 days; P = 0.85). 30 day mortality was also similar, 22% vs 24%, respectively; (OR, 0.90; 95% CI, 0.594 to 1.363; P=0.62). At 180 days, again there were similar rates of death; 40.5% vs 37.8% (difference, 2.7%; 95% CI, −11.3% to 5.8%; P=0.53). There were no differences in median lengths of either ICU (4 vs 4 days) or hospital stay (10 vs 9 days). There were also no differences in median values of coma/delirium-free days (4 vs 4) or kidney replacement therapy–free days (30 vs 30). There was no effect seen on time to treatment or any other prespecified variable. No serious adverse events were recorded in either group. When analysed using a per protocol approach rather than an intention-to-treat approach, again there were no significant differences seen in any outcome,

other than a lower mortality in those with urosepsis than in other sources of infection. At the planned interim analysis of 500 patients, the predictive probability of the intervention reaching the pre-defined threshold of declaring efficacy for the primary outcome was 30.7%.

Critique

The VICTAS trial appears to be a robust endeavour, but leaves some issues to consider. The question posed by the trial is both important and current, but differs subtly from other trials in the field.

Firstly, when compared with the original retrospective Marik study, the population differs slightly, with the Marik cohort including patients with a procalcitonin level ≥ 2 ng/mL and allowing permissive hyperglycaemia. Procalcitonin is a pro-hormone of calcitonin, and although levels increase during periods of stress, such as trauma or myocardial infarction, they increase to a greater extent during bacterial sepsis. Procalcitonin is used as a predictive marker of the probability of bacterial infections. A recent individual patient data level meta analysis based on 4482 patients from 11 randomised controlled trials examining the effect of procalcitonin-guided antibiotic therapy on mortality in critically ill patients with infection reported a slightly lower 30 day mortality; 21.1% vs 23.7%; (adjusted odds ratio, 0.89, 95% CI, 0.8 to 0.99; P = 0.03). Given the difficulties with identifying true infection in critically ill patients, it is possible the inclusion of an enrichment strategy such as this may have better identified a group of patients with the biochemical disturbances likely to be rectified by the combination of vitamin C, hydrocortisone and thiamine. However, the enormous effect size identified in the original study suggests if the interventions were effective, some signal of benefit would be apparent in 501 patients.

Whether a possible interaction with glycaemic levels exists is also interesting to consider. Both groups in the Marik study were managed with “permissive hyperglycaemia”, although it is unclear exactly what threshold(s) this refers to. Tight glycaemic control, in the range of 4.1 to 6.0 mmol/L has been shown to be harmful, due to the propensity to induce hypoglycaemia and neuroglyopaenia.[3] Whether a slightly high blood glucose level than the widely recommended 6 to 10 mmol/L range may be beneficial for general critically ill patients appears unlikely, but has been proposed for the subgroup of critically ill patients with pre-existing type 2 diabetes.[4] In the VICTAS trial, one-third of patients were diabetic (intervention, 31% vs control, 33%). The administration of stress dose hydrocortisone to patients in septic shock induces higher blood glucose levels.[5] Treatment with boluses doses of hydrocortisone induce greater changes than a continuous infusion. Despite the propensity for greater alterations in insulin therapy, no clinical effects were noted from this high glycaemic variability. The

LUCID trial compares a conservative glycaemic target of 6 to 10 mmol/L with a liberal target range of 10 to 14 mmol/L in critically ill patients with type 2 diabetes. The results were published on May 24th in the *American Journal of Respiratory and Critical Care Medicine*.[6] Less patients in the liberal group had an episode of hypoglycaemia (5% vs 18%; incident rate ratio, 0.21; 95% CI, 0.09 to 0.49; P<0.001), which was the primary outcome. However, patient centred outcomes were not improved, including mortality at day 90 (liberal group, 29.5% vs conservative group, 24.9%; difference, 4.6%; 95% CI, -3.9 to 13.2%; P=0.29).

Another issue pertaining to a high blood glucose range is the effect of high serum levels of vitamin C on point-of-care glucometers, with resultant falsely-high serum glucose readings. This interaction arises due to electron donation from the vitamin C molecule to the sensing electrode, rather than from glucose, and is not present in laboratory methods for measuring glucose.[7] This has been documented in case series of patients with severe burns > 30% total body surface area receiving an intravenous infusion of 66 mg/kg/hour (100 to 150 g/day).[8,9] Two small case series in patients with sepsis receiving the more standard dose of 6 g/day have also reported interactions between vitamin C administration and point-of-care glucose measurements, although the exact clinical implications of these differences are less certain than in the higher dose studies.[7,10] While the potential for overtreating incorrect glucose levels with insulin risks episodes of hypoglycaemia, which are known to be harmful in the critically ill,[3] there was no sign of a significant hypoglycaemic effect in the VICTAS trial. Notably, a point-of-care glucometer approved for use in the setting of high serum vitamin C levels was used in the VICTAS trial, although it is unclear if this was the case in the original Marik study. A case report from the large Canadian LOVIT trial, examining vitamin C in 800 patients with septic shock, described this interaction lasting up to 6 days after the cessation of vitamin C therapy.[11]

There was a degree of contamination, with 32% of patients in the control group receiving open label corticosteroids. As steroid therapy has been shown to reduce the duration of vasopressor therapy,[12] as well as mortality,[13] this contamination makes it more likely a null result may be seen. The VITAMINS trial[14] protocolised the use of stress dose steroids in both groups for this reason. Despite this contamination, there was a high rate of concordance with the protocol for the administration of the study drugs, as already described.

The study drugs were administered at a median of 14.7 hours after randomisation. This compares to times of 8 - 9 hours from arrival in the emergency department to study drug administration in the ATESS trial, 9.9 hours from arrival in the emergency department to study drug administration in the ORANGES trial, 13.5 hours from commencement of

vasopressors to study drug administration in the ACTS trial, within 6 hours of recruitment in CITRIS-ALI, with a recruitment window of 24 hours, and 12 hours to vitamin C administration in the VITAMINS trial. Given the retrospective nature of the original Marik study, time to therapy was not described. No effect from time to treatment was identified in VICTAS, VATIMINS[15] or ACTS.[16]

In summary, if an effect of the size described in the original trial existed, it would easily be identified in this trial of 501 critically ill patients with a high severity of illness. In keeping with the other recent randomised controlled trials investigating the combination of vitamin C and thiamine, with or without hydrocortisone, no such effect exists. If the LOVIT trial fails to report benefit, the evidence will likely strongly be in favour of no discernible efficacy from vitamin C and thiamine.

	Time from Randomisation to Study Drug Administration	Comment
VICTAS	14.7	Recruitment within 24 hours of onset of organ support
VITAMINS	Within 12 hours 22.1 hours (correspondence)	Recruitment within 24 hours of onset of septic shock ICU admission to randomisation 13.7 hours
ATESS	9.9	From arrival in the ED
ACTS	13.5	From start of vasopressors
CITRIS-ALI	Within 6 hours of enrolment	48 hour recruitment window
Marik	Not Reported	

Table 6. Time from randomisation to study drug administration

Where this sits in the body of evidence

In 2016, Paul Marik published the results of a small single centre, retrospective, before-and-after study, documenting the effects of the combination of intravenous vitamin C (1.5 g 6 hourly), thiamine (200 mg 12 hourly) and hydrocortisone (50 mg 6 hourly) in patients with sepsis or septic shock and a procalcitonin level ≥ 2 ng/mL .[1] Forty-seven consecutive patients treated with the combination therapy were identified during a 7 month period and compared with a historical control group of 47 patients who did not receive vitamin C or thiamine. The hospital mortality rate in the intervention group was markedly lower, 8.5% vs 40.4%; OR, 0.13; 95% CI, 0.04 to 0.48; P = 0.002. The veracity of these data have subsequently been questioned.[17]

Fujii and colleagues completed the first randomised trial investigating vitamin C and thiamine in patients with sepsis.[14] As the ADRENAL[12] and APPROCHSS[13] trials had shown benefit with corticosteroids in sepsis, the trialists mandated both groups receive hydrocortisone 50 mg every 6 hours as standard care and randomised patients to either open label intravenous vitamin C (1.5 g 6 hourly) and thiamine (200 mg 12 hourly) or matching placebo. The trial took place in 10 ICUs in Australia, Brazil and New Zealand between 2018 and 2019 and randomised 216 patients, analysing 211 after completion of the consent process. There was no difference in the primary outcome of time alive and vasopressor free up to day 7; intervention group, 122.1 hours (IQR, 76.3 to 145.4) versus control group, 124.6 hours (82.1 to 147.0); median of all paired differences, –0.6 hours (95% CI, –8.3 to 7.2 hours; P = 0.83). There were no significant differences in any patient centred secondary outcomes, including ICU mortality (21% vs 19%), 28 day mortality (22.6% vs 20.4%), 90-day mortality (30% vs 25%), or lengths of organ support, ICU-free days or hospital admission (12.3 vs 12.3 days).

In two American non-teaching hospitals in 2018 and 2019, Iglesias and colleagues performed the blinded, randomised placebo-controlled ORANGES trial, comparing the combination of hydrocortisone (50 mg 6 hourly), vitamin C (1.5 g 6 hourly) and thiamine (200 mg 12 hourly) with placebo in 137 patients with sepsis or septic shock and found a quicker resolution of shock (co-primary outcome) in the intervention group (27 ± 22 vs 53 ± 38 hours; P < 0.001), no significant change in the secondary co-primary outcome of change in SOFA score at 72 hours, and no differences in patient centred outcomes including ICU mortality (9% vs 14%) and hospital length-of-stay (11.5 vs 11.0 days).[18]

The Chinese single centre, blinded, randomised, placebo controlled HYVCTTSSS trial compared the combination of hydrocortisone (50 mg 6 hourly), vitamin C (1.5 g 6 hourly) and thiamine (200 mg 12 hourly) with placebo in 80 patients with sepsis or septic shock and found no difference in the primary outcome of 28-day mortality (intervention group, 27.5% vs control, 35%; RR, 0.79; 95% CI, 0.41 to 1.52; P=0.47) or patient centred secondary outcomes, including duration of vasopressors (46 vs 58.5 hours) or duration of mechanical ventilation (126.5 vs 94.5 hours).[19] The change in SOFA score at 72 hours was significantly decreased in the intervention group (3.5 vs 1.8; P=0.02).

The ATESS trial randomised 111 patients with septic shock in four South Korean emergency departments between 2018 and 2019 to receive either vitamin C (50 mg/kg, maximum single dose 3g) and thiamine (200 mg) in a blinded fashion every 12 hours, for up to 48 hours, or matching saline placebo.[20] Hydrocortisone and vasopressin were added when patients reached a dose of noradrenaline of 0.2 µg/kg/min. Despite higher serum levels of both vitamin C and thiamine being achieved at 72 hours in the

intervention group, there were no significant differences in any outcome, including the primary outcome of change in SOFA score at 72 hours (intervention group, 3 vs control group, 3; difference 0, 95% CI, 2 to 1; P=0.96) or secondary outcomes including 28 day mortality (20.8% vs 15.5%), vasopressor-free days (11 vs 11), ventilator-free days (11 vs 11) or ICU length of stay (5 vs 5.5 days).

Moskowitz and colleagues reported the results of the ACTS trial in 2020. This multi-centre trial recruited 205 patients with septic shock at 14 centres in the USA between 2018 and 2019 and, in blinded fashion, compared the combination of hydrocortisone (50 mg 6 hourly), vitamin C (1.5 g 6 hourly) and thiamine (200 mg 12 hourly) with placebo for up to 4 days.[16] There was no difference in the primary outcome of change in SOFA score at 72 hours (intervention group, 4.4 vs control, 5.1; adjusted mean difference 0.8; 95% CI, 1.7 to 0.2; P = 0.12). Other than an improvement in median number of shock free days (5 vs 4; difference 1; 95% CI, 0.2 to 1.8; P=0.02), there were no improvements in secondary outcomes including 30 day mortality (34.7% vs 29.3%) renal failure (31.7% vs 27.3%), ventilator-free days (6 vs 6), ICU-free days (22 vs 21) or survivors-discharged home (46.6% vs 46.1%).

The CITRIS-ALI trial compared intravenous vitamin C (50 mg/kg) with matching placebo 6 hourly for up to 96 hours, in 167 patients with sepsis and ARDS, at 7 medical ICUs in the USA, between 2014 and 2017.[21] 103 patients (62%) completed the study to day 60. There was no significant difference in the co-primary outcomes of change in mean modified SOFA score at 96 hours (intervention group, 3 vs control group, 3.5 points; difference, −0.10; 95% CI, −1.23 to 1.03; P = 0.86), or C-reactive protein levels at 168 hours (54.1 vs 46.1 µg/mL; difference, 7.94 µg/mL; 95% CI, −8.2 to 24.11; P = 0.33) or thrombomodulin levels at 168 hours (14.5 vs 13.8 ng/mL; difference, 0.69 ng/mL; 95% CI, −2.8 to 4.2; P = 0.70). Amongst the 46 prespecified secondary outcomes, 43 were similar between the two groups, although these analyses did not account for multiple testing. Exploratory results reported benefits with vitamin C in 28-day mortality rates (29.8% vs 46.3%; difference, 16.58%; 95% CI, 2% to 31.1%), ventilator-free days (13.1 vs 10.6; mean difference, 2.47; 95% CI, −0.90 to 5.85; P = 0.15) and ICU-free days to day 28 (10.7 vs 7.7; mean difference, 3.2; 95% CI, 0.3 to 5.9; P = 0.03).

The LOVIT trial, the largest yet trial of the combination of vitamin C, thiamine and hydrocortisone in patients with septic shock, is due to be presented at the Critical Care Reviews Meeting 2022, in June.[22] A minimum of 800 ICU patients receiving vasopressors are planned to be enrolled. The primary outcome is a composite of death or persistent organ dysfunction, defined as ongoing need for vasopressors, invasive mechanical ventilation, or new and persisting renal replacement therapy at day 28. The trial will

have an anticipated 80% power to detect a 10% absolute risk reduction (from 50% to 40%) in the primary outcome.

Should we administer the combination of vitamin C, thiamine and hydrocortisone to patients with sepsis or septic shock?

No, pending the outcome of the LOVIT trial, there is no consistent signal of benefit from a range of randomised controlled trials, including VICTAS.

References

1. Marik PE, Khangoora V, Rivera R, Hooper MH, Catravas J. Hydrocortisone, Vitamin C, and Thiamine for the Treatment of Severe Sepsis and Septic Shock: A Retrospective Before-After Study. Chest 2017;151(6):1229–38.

2. Marik PE. Vitamin C for the treatment of sepsis: The scientific rationale. Pharmacol Ther 2018;189:63–70.

3. Nice-Sugar Study Investigators. Intensive versus conventional glucose control in critically ill patients. N Engl J Med 2009;360(13):1283–97.

4. Bellomo R. Acute glycemic control in diabetics. How sweet is optimal? Pro: Sweeter is better in diabetes. J Intensive Care 2018;6(1):1–3.

5. Loisa P, Parviainen I, Tenhunen J, Hovilehto S, Ruokonen E. Effect of mode of hydrocortisone administration on glycemic control in patients with septic shock: a prospective randomized trial. Crit Care 2007;11(1):1–9.

6. Poole AP, Finnis ME, Anstey J, et al. The Effect of a Liberal Approach to Glucose Control in Critically Ill Patients with Type 2 Diabetes: A multicenter, parallel-group, open-label, randomized clinical trial. Am J Respir Crit Care Med 2022 [cited 2022 Jun 2]; Available from: https://www.atsjournals.org/doi/10.1164/rccm.202202-0329OC

7. Howell AP, Parrett JL, Malcom DR. Impact of high-dose intravenous vitamin C for treatment of sepsis on point-of-care blood glucose readings. J Diabetes Sci Technol 2021;15(2):309–16.

8. Sartor Z, Kesey J, Dissanaike S. The effects of intravenous vitamin C on point-of-care glucose monitoring. J Burn Care Res 2015;36(1):50–6.

9. Kahn SA, Lentz CW. Fictitious hyperglycemia: point-of-care glucose measurement is inaccurate during high-dose vitamin C infusion for burn shock resuscitation. J Burn Care Res 2015;36(2):e67–71.

10. Smith KE, Brown CS, Manning BM, et al. Accuracy of Point-of-Care Blood Glucose Level Measurements in Critically Ill Patients with Sepsis Receiving High-Dose Intravenous Vitamin C. Pharmacother J Hum Pharmacol Drug Ther 2018;38(11):1155–61.

11. Lachance O, Goyer F, Adhikari NK, et al. High-dose vitamin-C induced prolonged factitious hyperglycemia in a peritoneal dialysis patient: a case report. J Med Case Reports 2021;15(1):1–4.

12. Venkatesh B, Finfer S, Cohen J, et al. Adjunctive Glucocorticoid Therapy in Patients with Septic Shock. N Engl J Med 2018;378:797–808.

13. Annane D, Renault A, Brun-Buisson C, et al. Hydrocortisone plus Fludrocortisone for Adults with Septic Shock. N Engl J Med 2018;378(9):809–18.

14. Fujii T, Luethi N, Young PJ, et al. Effect of vitamin C, hydrocortisone, and thiamine vs hydrocortisone alone on time alive and free of vasopressor support among patients with septic shock: the vitamins randomized clinical trial. JAMA 2020;323(5):423–31.

15. Long MT, Kory P, Marik P. Vitamin C, hydrocortisone, and thiamine for septic shock. JAMA 2020;323(21):2203–4.

16. Moskowitz A, Huang DT, Hou PC, et al. Effect of ascorbic acid, corticosteroids, and thiamine on organ injury in septic shock: the ACTS randomized clinical trial. JAMA J Am Med Assoc 2020;324(7):642–50.

17. Infamous Vitamin C Study May Rely on Fraudulent Data [Internet]. 2022 [cited 2022 Jun 2];Available from: https://www.medpagetoday.com/special-reports/exclusives/97865

18. Iglesias J, Vassallo AV, Patel VV, Sullivan JB, Cavanaugh J, Elbaga Y. Outcomes of Metabolic Resuscitation Using Ascorbic Acid, Thiamine, and Glucocorticoids in the Early Treatment of Sepsis: : The ORANGES Trial. Chest 2020;158(1):164–73.

19. Chang P, Liao Y, Guan J, et al. Combined treatment with hydrocortisone, vitamin C, and thiamine for sepsis and septic shock (HYVCTTSSS): A randomized controlled clinical trial. Chest 2020;158(1):174–82.

20. Hwang SY, Ryoo SM, Park JE, et al. Combination therapy of vitamin C and thiamine for septic shock: a multi-centre, double-blinded randomized, controlled study. Intensive Care Med 2020;46(11):2015–25.

21. Fowler AA, Truwit JD, Hite RD, et al. Effect of Vitamin C Infusion on Organ Failure and Biomarkers of Inflammation and Vascular Injury in Patients With Sepsis and Severe Acute Respiratory Failure: The CITRIS-ALI Randomized Clinical Trial. JAMA 2019;322(13):1261–70.

22. Masse M-H, Ménard J, Sprague S, et al. Lessening Organ dysfunction with VITamin C (LOVIT): protocol for a randomized controlled trial. Trials 2020;21(1):1–12.


My
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Summarising, critiquing and putting into context the best critical care trials of 2021

Written by

Ross McMullan | Neil Cody | Jon Silversides | Chris Nutt | Rob Mac Sweeney