Critical Care Reviews Book 2023

The Best Critical Care Trials of 2022

First Edition


Critical Care
Reviews

This book has been generously sponsored by the Critical Care Charitable Trust Fund of the Belfast Health and Social Care Trust

About

The Critical Care Reviews Book 2023 seeks to summarise, critique and put in context the best critical care trials of 2022. For the first time, a number of international contributors have assisted with writing the book. It is also not yet complete, as there are many more trials to be added. Unfortunately, we ran out of time to include them. We aim to put out a second edition of this year's book later in the Autumn

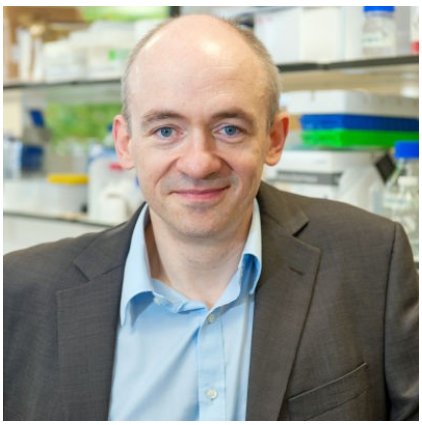
We hope you enjoy this work and find it useful in your daily practice. Please read the disclaimer at the bottom of this page.

The print version of the book has been very generously sponsored by the Critical Care Trust Fund of the Belfast Health and Social Care Trust. Every registered in-person 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.

Rob Mac Sweeney
Critical Care Reviews

Belfast,
June 2023

Foreword



It is a honour to write the foreword for the 2023 Critical Care Reviews Book.

While all knowledge has the potential to impact patient care, a well-designed and conducted randomised controlled clinical trial is undoubtedly the most likely to inform patient care. However, the number of new clinical trials which are published is beyond the capacity for a busy clinician to read and keep up-to-date with. Many of us may only read the abstract which will miss important contextual factors that impact the interpretation of trial results. An additional challenge is that clinical trials are increasingly using approaches which clinicians may be less familiar with in terms of both design and analyses. This means there is a need to have methodological expertise, and more importantly time, to critically appraise new trials to determine what should change clinical practice. Therefore this book, which reviews the most recent and important critical care trials, is an invaluable guide for clinicians to understand how these trial data should be implemented to improve patient outcomes. The book is well written, and presents each trial in a structured manner, providing a synopsis and critique of the trial, highlighting where the new data sits in the current body of evidence and importantly does this without bias.

The 2023 Critical Care Reviews Meeting book should be essential reading for every ICU clinician.

The commitment to produce this book by Rob and the team is unparalleled. I would also encourage you all to consider supporting Critical Care Reviews, either through a regular subscription or one-off donation, to help Rob continue to successfully deliver on his aim to share science widely for the benefit of all.

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AID-ICU

Andersen-Ranberg NC, Poulsen LM, Perner A, Wetterslev J, Estrup S, Hästbacka J, et al. Haloperidol for the Treatment of Delirium in ICU Patients. N Engl J Med 2022; 387:2425-2435

Introduction

Delirium is a common and serious problem in the Intensive Care Unit (ICU), with studies showing a variable incidence, ranging over 80% in critically ill, mechanically ventilated patients.[1] It can be categorised into three main phenotypes: hyperactive, hypoactive, and mixed, with hypoactive being the most common and often under-diagnosed due to its less overt presentation.

The consequences of delirium in ICU patients are significant and multifaceted. Delirium has been associated with prolonged hospital stay, increased mortality, poor functional recovery, and long-term cognitive impairment that can persist after discharge from the ICU and increase the requirement for long term care or nursing home dependency.[2]

In terms of treatment, both non-pharmacological and pharmacological interventions have been explored. Non-pharmacological interventions including environmental modification, reorientation, and sleep promotion have been shown to reduce the incidence and duration of delirium. As for pharmacological interventions, antipsychotics such as haloperidol are frequently used, but their effectiveness is not clear. Three randomised controlled trials to date have failed to demonstrate efficacy in the ICU setting.[3–5]

Haloperidol is a typical antipsychotic that works primarily by blocking dopamine receptors, particularly D2 receptors, in the brain. This reduction in dopaminergic activity is believed to help manage the symptoms of delirium, though the exact mechanism in this context is not fully understood. Being an effective motor retardant, its role may be in management of the agitated, hyperactive delirious patient, reducing the risk of self harm. However, in the absence of a pharmacological therapy for the management of delirium, an evidence gap exists for a common and serious problem.

Synopsis

The AID-ICU trial (Agents Intervening against Delirium in the Intensive Care Unit) tested the hypothesis that in adult ICU patients diagnosed with delirium, the administration of

haloperidol, compared to a placebo, would increase the number of days alive and out of the hospital within 90 days post-randomization.
This was an investigator-initiated, international, multicentre, randomised, blinded, parallel-group trial and ran between June, 2018, and April, 2022, at 18 general ICUs in Denmark, Finland, the United Kingdom, Italy, and Spain.

Eligible patients were adults, acutely admitted to the ICU, and suffering from delirium, which was diagnosed using the validated screening tools the Confusion Assessment Method for the ICU (CAM-ICU) and the Intensive Care Delirium Screening Checklist (ICDSC). Trial specific exclusion criteria included a contraindication to haloperidol, Parkinson's disease, extrapyramidal symptoms, known QTc prolongation, a history of tardive dyskinesia, delirium tremens, chronic use of an atypical antipsychotic agent, the presence of a non-pharmacological coma, previous ventricular arrhythmia or torsades de pointes, uncorrected hypokalaemia, antipsychotic treatment in the ICU prior to inclusion were not eligible, permanently incompetent patients, such as those with dementia, and those for whom delirium assessment was not possible, such as due to coma or language barriers.

Patients with a positive delirium score were screened for enrolment. The randomisation process was centralised and web-based, using a computer-generated allocation sequence list, with randomly varying block sizes and stratification according to trial site and delirium motor subtype (hyperactive or hypoactive). The allocation sequence list was known exclusively to the data manager at the Copenhagen Trial Unit and was unknown to the investigators. The randomisation was performed in a 1:1 ratio, assigning patients to either the haloperidol group or the placebo group. The trial medications were visibly identical. Patients were screened for delirium twice daily.

Haloperidol was administered intravenously at a dose of 2.5 mg three times daily. The control group received a matching placebo, which was isotonic saline. The trial allowed for additional doses of haloperidol or placebo as needed, up to a maximum of 20 mg per day. If further pharmaceutical intervention was required beyond the maximum daily dose of the study drug, the clinicians had the discretion to choose from a set of "escape" medications. These included intravenous propofol, benzodiazepines, or an α2-agonists. If a patient experienced an adverse reaction, the trial intervention would be discontinued, and the patient treated according to usual care other than haloperidol. The trial medication was continued until the patient was free from delirium on two successive assessments within 1 day, was discharged from the ICU, or for 90 days. If a patient was discharged from the ICU but readmitted within the 90 day intervention period, the trial medication was restarted.

The primary outcome of the trial was days alive and out of the hospital within 90 days. Secondary outcomes included days alive without delirium or coma, days alive without mechanical ventilation, one year mortality, use of escape medicine, functional scores and a health economic analysis. Subgroups included trial site, the motor subtype of delirium (hyperactive or hypoactive), the type of ICU admission (medical or surgical), gender (female or male), age (younger than 69 years or 69 and older), presence of one or more risk factors for delirium (yes or no), and the severity of the disease as indicated by the SMS-ICU score (less than 25 or 25 and above).

Based on the AID-ICU cohort study, the trialists extrapolated the distribution of days alive and out of hospital at 90 days to the placebo group. It was hypothesised that the administration of haloperidol would produce a 15% decrease in the incidence of in-hospital death and a shorter length of hospital stay compared to placebo. The combined effect was anticipated to produce an 8% increase in the mean number of days alive and out of the hospital. 1000 patients were required to detect such a difference with a power of 90% at a 5% significance level. An interim analysis was performed when data for the primary outcome was available for 500 patients.

1738 patients were screened, 738 were excluded, and 1000 were randomised, 510 to the haloperidol group and 490 to the placebo group. The most common reasons for exclusion from the trial were receipt of an antipsychotic in the ICU (n=427), contraindication to haloperidol (n=130) and prior antipsychotic use (n=107). 491 of the haloperidol group and 472 of the control group underwent analysis for the primary outcome.

The groups were similar at baseline. A typical patient was male (~66%), age ~70, and had a medical reason for ICU admission (~65%). Approximately 2/3rds of patients were receiving invasive mechanical ventilation, half were receiving a vasopressor or inotrope and 15% were receiving renal replacement therapy. The CAM-ICU screening tool was used in most patients (~78%). Patients were typically admitted to ICU within a day of hospital admission and recruited into the trial 4 days after ICU admission.

Study drug administration was largely similar in both group, with median durations of the study drugs of ~3.5 days, and a median daily dose of ~3.5 administrations. The median total number of doses received was ~13, and median cumulative total dose ~32.5 mg. There was no apparent difference in the use of rescue medications, open label antipsychotics (~13%) or restraints (~2%).

There was no significant difference in the primary outcome, the number of days alive and out of the hospital by day 90 – haloperidol group, 35.8 vs control group, 32.9

(adjusted mean difference, 2.9; 95% CI, −1.2 to 7.0; P = 0.22). No effect was seen in the prespecified subgroups. Mortality was lower in the haloperidol group: 36.3% vs 43.3%; aRR, 0.84; 95% CI, 0.72 to 0.98. Secondary outcomes were similar between groups, including Days alive without delirium or coma (57.7% vs 52.6%), Days alive without mechanical ventilation (57.9% vs 53.9%), serious adverse reactions (2.2% vs 1.9%) and use of rescue medication (57.5% vs 62.1%).

Critique

AID-ICU was a robust clinical trial from an experienced trials group with a worldwide reputation for excellence. As such, the trial design and execution was robust and allows confidence in the results. It was large, multi-centre, placebo-controlled, and blinded, with 98.7% of patients available for analysis of the primary outcome. Despite such an excellently run trial, there was no significant difference between the haloperidol and placebo groups in the primary outcome, which was the number of days alive and out of the hospital at 90 days after randomisation.

Interestingly, the trial did observe a lower mortality at 90 days in the haloperidol group compared to the placebo group (36.3% vs 43.3%). This suggests a possible mortality effect of haloperidol, although the trial was not specifically powered to detect this. Such an effect could have major implications for the management of delirium patients, particularly in the ICU where mortality rates are high. However, the exact reason for this observed mortality effect is not clear from the trial and would need to be investigated in future studies.

Whether different dosing would have produced a different outcome is unknown, but the AID-ICU team had an evidence-base to support their choice. Similarly, whether a different anti-psychotic may be effective is an active question, but was outside the scope of AID-ICU to answer.

Researching a syndrome like delirium is challenging due to its multifactorial nature, varying presentation, and the difficulty in making a definitive underlying diagnosis. This makes it hard to determine the exact effect of a treatment like haloperidol. Additionally, the population of patients with delirium is often heterogeneous, with varying underlying conditions, which can further complicate the analysis of trial results. Classifying by hyperactive or hypoactive phenotypes is difficult,as most patients have a mixed form, alternating between hyper- and hypo-active delirium. The trialists did use validated screening tools, reducing variability and bias in the assessment of the presence of delirium.

As for the mechanism of action of haloperidol, it is believed to work by blocking D2 dopamine receptors in the brain. This can reduce the symptoms of delirium, which are thought to be associated with an imbalance of neurotransmitters like dopamine. However, the exact mechanism by which haloperidol might exert a mortality effect is not clear and was not directly addressed in the AID trial.

The interpretation of a trial with a null or inconclusive primary outcome can be challenging. Traditionally, all lower outcomes are considered hypothesis generating. The recent trend for reanalysing trials using a Bayesian method allows a probabilistic approach to evaluating the primary outcome. The AID-ICU trialists had pre-specified such an analysis and it was strongly positive for the likelihood of benefit from haloperidol in terms of days alive and out of hospital, with a 92% for any benefit and 82% for clinically important benefit. The mortality effect was even more marked, with a 99% probability for any benefit and 94% for clinically important benefit.

12 questions have been proposed to help deal with this issue of a null primary outcome and statistically significant other outcomes.[6] These questions include whether other outcomes report positive findings and if there is a strong biological rationale that favours the treatment. For AID-ICU, the secondary outcomes are inconclusive, including the possibility of both benefit and harm. Although the design of the trial did not address the biological effect of haloperidol in delirium, it was notable that both groups appear to have similar rates of rescue medications, open-label antipsychotics and restraints. The trialists have correctly played down the potential significance of this mortality effect, but it remains tantalising.

Body of Evidence

The HOPE-ICU trial[4] was a double-blind, placebo-controlled randomised investigation aimed at determining if early intervention with haloperidol could reduce the time critically ill patients spent with delirium or coma. The trial took place in a general adult ICU, where critically ill patients who needed mechanical ventilation within 72 hours of admission were enrolled. Patients were randomly assigned to receive either haloperidol 2.5 mg or a saline placebo intravenously every 8 hours. The administration of the study drug was halted either on ICU discharge, after two consecutive days without delirium or coma, or after a maximum of 14 days of treatment. The primary measure of interest was the number of days in the first 14 days post-randomisation during which the patient remained alive, delirium-free, and not in a coma. Patients who died within this 14-day period were noted as having zero days free of delirium and coma. Out of the 142 patients that were randomised, 141 were included in the final analysis; 71 received haloperidol and 70 were given the placebo. There was no significant difference between the two groups in the median number of days alive without delirium or coma (5 days

[IQR 0–10] *vs* 6 days [0–11] days; p=0.53). The most frequent side effects noted were over-sedation (11 vs six) and QTc prolongation (7 vs 6). Importantly, no serious adverse events related to the study drug were reported.

The MIND trial[3] was a randomized, double-blind, placebo-controlled study conducted at six tertiary care medical centres in the United States, aiming to ascertain the feasibility of a placebo-controlled trial for antipsychotics in the intensive care unit (ICU). It also hypothesised that antipsychotics would enhance the number of days patients lived without delirium or coma. The study involved 101 mechanically ventilated patients from medical and surgical ICUs. These patients were randomly assigned to receive haloperidol, ziprasidone, or a placebo every six hours for a maximum of 14 days. The frequency of drug administration was adjusted twice daily based on the status of delirium, level of sedation, and side effects. The primary outcome was the number of days patients lived without delirium or coma. The findings showed that during the 21-day study period, there were no significant differences in the median number of days patients lived without delirium or coma among the haloperidol (14.0 days), ziprasidone (15.0 days), and placebo (12.5 days) groups. Secondary clinical outcomes, such as ventilator-free days, hospital length of stay, and mortality, also did not significantly differ among the groups. Symptoms consistent with akathisia were reported by 29% of patients in the haloperidol group, 20% in the ziprasidone group, and 19% in the placebo group. The overall measure of extrapyramidal symptoms was similar across all treatment groups.

MIND-USA[5] was an American multi-centre, blinded, randomised controlled trial assessing haloperidol and ziprasidone in 1183 critically ill patients with delirium. 566 patients developed delirium and were eligible to receive the study drugs (haloperidol, n=192;, ziprasidone, n=190; or placebo, n=184). Haloperidol was administered to a maximum daily dose of 20 mg and ziprasidone to a maximum daily dose of 40 mg. Doses could be halved or doubled as necessary, depending on the presence of delirium. Study drugs were administered for a median of 4 days. There was no significant difference between the groups in the occurrence of the primary outcome, the median number of days alive without delirium or coma (placebo, 8.5; haloperidol, 7.9 and ziprasidone, 8.7; P=0.26). Secondary endpoints and harms were also similar between groups.

A Bayesian analysis[7] of the "AID-ICU" trial suggested a potential benefit of haloperidol treatment. The mean difference for days alive and out of the hospital to day 90 (primary outcome) was 2.9 days with a 92% probability of any benefit and an 82% probability of a clinically important benefit. The risk difference for mortality was -6.8 percentage points with a 99% probability of any benefit and a 94% probability of a clinically important

benefit. The adjusted risk difference for serious adverse reactions was 0.3 percentage points with a 98% probability of no clinically important difference.
The 2018 Clinical Practice Guidelines for the Prevention and Management of Pain, Agitation/Sedation, Delirium, Immobility, and Sleep Disruption in Adult Patients in the ICU recommends against the use of haloperidol for both prophylaxis and treatment of delirium. This is largely based on two randomised controlled trials, MIND[3] and HOPE-ICU.[4]

Should we routinely treat critically ill patients with delirium with haloperidol

It is unclear. Three smallish trials have failed to identify benefit with this approach, while a fourth, AID-ICU, has produced a mixed result, with a null primary outcome but suggestive results on a Bayesian analysis

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Resuscitation Trials

DOSE VF

Cheskes S, Verbeek R, Drennan IR, McLeod SL, Turner L, Pinto R, et al. Defibrillation Strategies for Refractory Ventricular Fibrillation. N Engl J Med 2022;387:1947-1956

Introduction

Cardiac arrest remains a leading cause of death in the developed world, with an incidence of approximately 67 to 170 per 100,000 in Europe.[1] Refractory ventricular fibrillation occurs in less than 10% of all cardiac arrests but is believed to represent a subset of viable patients in whom good neurological outcomes can be achieved if the patient is successfully resuscitated. Treatment options in refractory ventricular fibrillation (VF) and pulseless ventricular tachycardia (pVT) have remained unchanged in recent years.

The most recent, widely generalisable study in the field is likely the 2016 ALPS study comparing anti-arrhythmic drugs to a placebo in shock-refractory cardiac arrest,[2] although other avenues such as extracorporeal membrane oxygenation[3–5] or beta-blockade[6] are of increasing interest. Cheskes et al. conducted DOSE VF to test a novel defibrillation strategy designed to lower the defibrillation threshold with a "conditioning" shock in double sequential defibrillation (DSED) or to target a different spatial region of fibrillatory myocardium with vector change (VC) defibrillation.

Synopsis

The Double Sequential External Defibrillation for Refractory Ventricular Fibrillation (DOSE VF) trial was an investigator-initiated, regional, multi-centre, open-label, cluster-randomised, controlled trial comparing double sequential defibrillation or vector change defibrillation with standard defibrillation in adults with refractory ventricular fibrillation in out-of-hospital cardiac arrest. The trial ran in six pre-hospital services (including approximately 4000 paramedics) in Ontario, Canada between March 2018 and May 2022. It was published in the New England Journal of Medicine on 6 November 2022.

Adult patients (over 17 years old) who had an out-of-hospital cardiac arrest of presumed cardiac cause with an initial rhythm of ventricular fibrillation or pulseless ventricular tachycardia AND who remained in VF/pVT despite three consecutive rhythm analyses and standard defibrillations (separated by two minutes of CPR each) were eligible for inclusion. Exclusion criteria included: traumatic cardiac arrest, drowning, hypothermia, hanging, suspected drug overdose, or patients with DNR directives.

Randomisation was performed at the level of the paramedic service; each of the six paramedic services switched to a different treatment arm every six months based on a random sequence generated prior to the start of the trial. Each participating paramedic service (cluster) had to switch to each treatment arm at least once during the trial.

Patients received standard ACLS level care; the first three non-study defibrillations were delivered via anterior-lateral pad placement. The fourth and all subsequent defibrillations were delivered in one of three ways according to the cluster's current treatment arm allocation. The control group continued standard defibrillation with pads in the anterior-lateral placement (i.e., no change from the first three defibrillations). The first intervention group, consisting of vector change (VC) defibrillation, saw the anterior defibrillation pad moved to the posterior, left mid-back; all subsequent defibrillations were delivered in this anterior-posterior configuration. The second intervention group—double sequential defibrillation (DSED)—required a second set of defibrillation pads applied in a standard anterior-posterior configuration, leaving the initial sets of pads undisturbed. Shocks, coming from pads connected to two different defibrillators, were administered in rapid succession (<1 second difference), but not simultaneously (so as to minimise potential damage to the defibrillators). The trial protocol specifies the anterior-lateral defibrillation to be delivered first, followed by the anterior-posterior shock. The fourth and all subsequent defibrillations were administered in this fashion for patients in this treatment arm.

The primary outcome was survival to hospital discharge. The authors sought to enrol 930 patients (310 patients per group) to provide 80% power at an alpha level of 0.05 to detect an 8% absolute increase in survival, from an anticipated baseline rate of 12% (for patients in refractory VF) to 20% in either of the intervention groups. The authors assumed an intra-cluster correlation of 0.010 and an inter-period correlation of 0.008 without correcting for multiplicity. Both intervention arms (VC and DSED) shared the common control group, and no correction to the P value of 0.05 was made for testing multiple treatments. No interim analyses were performed. The primary outcome was reported on an intention-to-treat basis; additional pre-specified calculations included a sensitivity analysis (assessing the actual treatment received irrespective of randomised assignment) and two per-protocol analyses (assessing patients who received the assigned treatment at any time after the third standard defibrillation and patients who received the assigned therapy no later than the fourth defibrillation). All outcomes were calculated with generalised linear models accounting for paramedic service and time enrolled in trial, as well as age, sex, and receipt of bystander CPR. No imputation was performed for missing data.

Pre-specified secondary outcomes included: termination of VF, return of spontaneous circulation (ROSC; defined as an organised cardiac rhythm and a palpable pulse or blood pressure), and good neurological outcome (mRS < 3).

450 patients were screened for enrolment, and 405 were ultimately enrolled. Reasons for exclusion included: not having VF as the first recorded rhythm, termination of VF prior to the third defibrillation, and DNR order. Randomisation was roughly balanced to the three treatment arms, with 33.6% to standard defibrillation, 35.6% to VC, and 30.9% to DSED. The delivery of the randomised treatment was moderate across treatment groups: 99.3% of patients received the assigned treatment in the standard defibrillation arm, 78.4% in the VC arm, and 85.6% in the DSED arm. The trial was stopped early, prior to reaching the enrolment target, on the recommendation of the data safety monitoring board due to operational challenges in maintaining prompt scene response times caused by the COVID-19 pandemic.

The mean age of patients enrolled in the study was 63.6 years, and 84.4% were men, with no significant difference between treatment arms. The arrest was witnessed and bystander CPR was provided in 60.3% and 54.4% of patients in the standard defibrillation arm; these key variables were 76.4%/62.5% in VC and 66.4%/56.8% in DSED.

The primary outcome occurred in 13.3% of patients assigned to standard defibrillation, 21.7% of patients in VC, and 30.4% in DSED. The adjusted relative risk ratio comparing DSED to standard treatment was RR, 2.21; (95% CI, 1.33 to 3.67) and VC to standard treatment: RR, 1.71; (95% CI, 1.01 to 2.88).

Survival with good neurological outcome closely resembled the primary outcome, RR, 2.21; (95% CI, 1.26 to 3.88) for DSED and RR, 1.48; (95% CI, 0.81 to 2.71) for VC. The magnitude of the effect size estimate for termination of VF was smaller: RR, 1.25; (95% CI, 1.09 to 1.44) and RR, 1.18; (95% CI, 1.03 to 1.36) for DSED and VC, respectively. The absolute occurrence of termination of VF was much higher than both ROSC or survival in all groups (e.g., 67.6% termination of VF, 26.5% ROSC in the control group). The effect size for ROSC was larger than that of termination of VF, but smaller than survival, in both DSED (RR, 1.72; 95% CI, 1.22 to 2.42) and VC (RR, 1.39; 95% CI, 0.97 to 1.99).

Critique

The single largest critique of DOSE VF is the unplanned early termination of the study. The pre-specified protocol did not call for interim analyses, and the study began with the intention of enrolling 930 patients. However, after 405 patients were enrolled, the data safety monitoring board stopped the study due to apparent concerns about prolonged

paramedic response times to the scenes of these out-of-hospital cardiac arrests. (These operational challenges were undoubtedly exacerbated by the COVID-19 pandemic; the trial was temporarily paused between April 2020 and September 2020 to allow participating prehospital services to respond to the pandemic, but the trial was terminated ~1.5 years later in May 2022.)

In one respect, it is remarkable that the efficacy of DSED was still demonstrated despite enrolling less than half of the patients anticipated. The pre-planned power calculation estimated an 8% absolute survival benefit for VC and/or DSED, which a priori sounded aggressive. Few interventions in the modern era of critical care medicine approach double-digit mortality benefits. Using the standard-of-care estimate of 12% survival for patients in refractory ventricular fibrillation, and planning for a 5% absolute difference in survival, that hypothetical trial would need to enrol 1554 patients (in a two-arm trial). That DSED significantly decreased mortality despite enrolling a quarter of this number in a three-arm trial speaks to how large the effect size truly is. Every 5.8 patients treated with DSED will result in one extra life saved (an NNT of 5.8).

While the results are compelling for DSED, more caution must be exercised with the interpretation of the vector change defibrillation arm. While nominally statistically significant (RR 1.71 for survival to hospital discharge), the confidence interval approaches 1 (1.01 to 2.88), and the fragility index is 1. In other words, had a single patient randomised to VC suffered a different outcome (i.e.: had a single extra patient not survived), the intervention would no longer have been statistically significant. A low fragility index is common in critical care trials[7] and was likely exacerbated by early termination and by simultaneously trialling two interventions.

Although a noteworthy statistical point, it is unclear how clinically relevant a low fragility index is in this case. By effect size estimates, DSED is the more efficacious defibrillation strategy in refractory VF and should likely be used preferentially when two defibrillators are available. In situations where DSED is unavailable, even if there is low confidence in the statistical significance of VC, it is unlikely to cause harm. 2020 AHA guidelines conclude, "It is reasonable to place defibrillation paddles or pads on the exposed chest in an anterolateral or anteroposterior position." Switching pad placement between two positions that are in widespread clinical use and which have equivalent efficacy for termination of VF[8] appears to have an overwhelmingly positive risk-to-benefit ratio.
In addition to early termination of the study, data from the previously published pilot RCT[9] was included in this analysis. The pilot RCT enrolled 152 patients, leaving 253 new patients enrolled in the interim. In a study analysis plan dated June 11, 2021 (prior to study termination and presumably prior to unblinding of the investigators given the lack of pre-specified interim analyses) uploaded with the trial registration on clinicaltrials.gov

(NCT04080986), study authors pre-specified their intent to combine pilot RCT data into the final analysis. There is no evidence to suggest that authors engaged in post-hoc data manipulation to obtain a significant result. [Assuming reported effect sizes of 13.3% survival in control and 30.4% in DSED, a study would need to enrol 90 patients in each arm to achieve an alpha of 0.05 at a power of 0.8. DOSE VF, independent of pilot data, enrolled 100 patients in the control arm and 70 in DSED.]

Some statisticians worry that early study termination may systematically overestimate intervention effect sizes.[10] However, this concern is most pronounced in studies terminated early for apparent superiority, whereas DOSE VF was terminated due to logistical challenges. It remains possible that a smaller sample size could lead to an inflated effect estimate due to stopping in a "random high". While not a specific critique of this trial, it is worth remembering that in randomised controlled trials in critical care, the original study often reports a larger effect estimate than subsequent reproduction studies/data can demonstrate.[11]

Perhaps the most relevant consequence of DOSE VF's early termination is in understanding the time-dependence of DSED. Paramedics administered the first intervention defibrillation approximately 18 minutes after the initial bystander call for emergency services. The data safety monitoring board opined that lengthening response times would prolong time-to-intervention and would introduce heterogeneity into the trial. However, these operational challenges faced by paramedic services in Ontario are not unique and are shared internationally, especially as pandemic-mediated effects on the healthcare workforce continue to ravage pre- and in-hospital care paradigms. For many EMS systems facing similar challenges, rural jurisdictions without easy access to a second crew with a second defibrillator, or emergency departments with EMS crews that will not have DSED in their protocols, the time-to-intervention will realistically be much longer than 18 minutes. If anything, the early termination of DOSE VF reduces the generalisability of the findings.

It is interesting that the number of shocks to first ROSC and time from EMS arrival to first ROSC are the same irrespective of treatment group (~5.5 shocks and ~15 minutes, respectively). This may suggest that defibrillation timing is essential to outcomes, and there is a critical period somewhere within the first 20-25 minutes of cardiac arrest for defibrillation to be most successful. In the refractory VF population, DSED (or VC) does not shorten the low-flow time, but instead appears to increase the proportion of patients with termination of VF/ROSC within this "early" 20–25-minute benchmark.

The high-quality pre-hospital care administered by the paramedics must be commended. Paramedics arrived on scene quickly (<8 minutes), administered the first defibrillation

within 3 minutes of arrival on scene, and provided high-quality chest compressions (peri-shock pause ~11 seconds, chest compression fraction ~80%, compression depth ~6 cm, compression rate ~110). Paramedics achieved ROSC within 15 minutes of assuming patient care and began transport to an emergency department 11 minutes later. The pre-hospital care in this study was efficient and time-sensitive, which is well-known to be the bedrock of cardiac arrest resuscitation and is essential for the success of any subsequent interventions.

The patient population in this study is well representative and should be broadly generalisable beyond the local sites where this trial was conducted. Patients were predominantly male (~80%) and in their mid-60s, with bystander-witnessed cardiac arrest in 60-75% of cases. Bystander CPR was administered in 55-60% of arrests. Groups were well balanced at baseline and in all other aspects of cardiac arrest care (e.g.: adrenaline administration, anti-arrhythmic administration, etc.).

Body of Evidence

The DOSE VF study represents the largest and most rigorously conducted trial to date on the topic of double sequential defibrillation. Prior to this study, the only randomised data came from the pilot study for this trial from the same authors.[9] VF termination and ROSC rates were similar to those reported presently; notably, however, further discussion of this 2020 data is redundant, as the data collected in the pilot was merged with the full-scale trial and reported again in this 2022 publication. The publication of the current paper makes the 2020 report obsolete.

The remaining body of evidence consists of non-randomised case series. A 2018 case-control study retrospectively evaluating 128 patients in refractory VF/pVT found no difference in survival to hospital admission (48.0% to 50.5%).[12] However, only 25 patients in this cohort received DSED. The time to first DSED defibrillation was similar between the Cheskes and this San Antonio study (3.9 shocks to first DSED vs. 4.5 shocks). An uncontrolled retrospective analysis of the same EMS system over the same time period (January 2013 – December 2015) similarly reported no neurologically-intact survival benefit for DSED over standard defibrillation (RR, 0.50; (95% CI, 0.15 to 1.72).[13]

A retrospective analysis of 18 months of data from the London Ambulance Service did not show clear benefit for DSED late in the course of refractory VF resuscitation.[14] Termination of VF was observed in 17/45 (37.7%) of DSED patients and 61/175 (34.8%) of standard care patients; however, patients in the DSED arm also received ~10 standard defibrillations, pointing towards a potential time-dependent effect of alternative defibrillation strategies.

A retrospective analysis of data from 2013-2016 from the Houston Fire Department (Texas, USA) found that in 71 patients receiving DSED and 239 receiving standard care, ROSC was lower for DSED, and survival to hospital discharge trended lower. [15]

A case series of seven patients,[16] twelve patients,[17] ten patients,[18] and various case reports[19,20] comprise the rest of the published literature. This was systematically reviewed in 2020 by Deakin et al.[21]

The DOSE-VF study may be leading the way for renewed attention towards optimising defibrillation in shockable arrhythmias. In addition to novel double sequential defibrillation strategies, manual pressure augmentation[22] (registered as a prospective clinical trial ACTRN12621000804886), which has seen success for external cardioversion in atrial fibrillation[23,24], aims to reduce the transthoracic impedance during defibrillation and deliver more energy to the myocardium. Hands-on defibrillation, to reduce the peri-shock pause, and real-time physiology-guided defibrillation timing (such as AMSA, NCT03237910) are other strategies under active investigation in the shockable cardiac arrest field.

Should we routinely administer double sequential defibrillation to adult patients in refractory ventricular fibrillation?

Yes, this trial provides randomized-controlled evidence that DSED improves patient survival.

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PRAGUE OHCA Study

Belohlavek J, Smalcova J, Rob D, Franek O, Smid O, Pokorna M 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):737-747

Introduction

Cardiac arrest remains a vexing problem in the developed world and was the third leading cause of death in Europe.[1] Options in refractory cardiac arrest that do not respond to the mainstays of current resuscitation - defibrillations, antiarrhythmics, adrenaline, and/or targeting reversible causes - remain quite limited. The authors sought to trial a new, hyperinvasive style of resuscitation that would combine multiple treatments aimed at optimising distinct physiological derangements in cardiac arrest. Other groups had trialled individual treatments within the bundle, with uninspiring or non-robust results at the time. Belohlavek and colleagues sought to conduct the first large RCT targeting better chest compressions, earlier neuroprotection, mechanical circulatory support, and early PCI into one intervention arm in the Prague OHCA Study.

Synopsis

The Prague OHCA study was an investigator-initiated, single-centre, randomised controlled trial comparing a bundle of early intra-arrest transport, extracorporeal cardiopulmonary resuscitation (ECPR, i.e.: VA-ECMO intra-arrest), and early coronary angiography with standard care in adult patients with refractory out-of-hospital cardiac arrest. The trial ran in a single EMS system and cardiac referral centre in Prague, Czech Republic between March 2013 and October 2020. It was published in JAMA on 22 February 2022.

Adult patients aged 18-65 with witnessed OHCA of presumed cardiac origin and unresponsive to at least five minutes of ACLS were eligible for inclusion in the study. A key additional inclusion criterion reads, "[Patient] is eligible for enrolment in the trial… when the ECPR team was available at the cardiac centre." Notable exclusion criteria included: unwitnessed arrest, presumed non-cardiac aetiology, pregnancy, obvious life-limiting co-morbidities, known DNR, and/or known baseline CPC >2.
Randomisation was performed via a web-based system when the treating physician or paramedic on the scene called the study coordinator. Randomisation was stratified by

sex (male/female) and age (predicted less than or greater than 45 years), with a block size of eight. The trial was unblinded to treating clinicians, patients, and their families; blinding ECMO is not feasible. However, the neurologist assessing CPC for the primary outcome was blinded to treatment allocation.

The intervention included transport to the cardiac centre catheterisation laboratory with ongoing mechanical chest compression (via LUCAS device), femoro-femoral VA-ECMO on the catheterisation lab table, and immediate invasive angiography and subsequent coronary intervention if indicated. Following completion of diagnostic and therapeutic catheterisation procedures, an antegrade perfusion cannula was placed in the ipsilateral limb, and heparin anticoagulation was titrated to achieve an aPTT of 50-70 seconds. The control arm continued to receive standard ACLS on scene, transporting to a hospital when ROSC was achieved. Mechanical chest compression devices became available to the control group part-way through the trial, and its application at the discretion of the emergency physician. Early invasive coronary angiography was "encouraged" in the control arm.

The primary outcome was neurologically intact survival at 180 days, defined as CPC 1 or 2. Assuming a six-month survival of 10% in the standard care group, 285 patients were required to identify a 15% absolute increase in neurologically intact survival, with 90% power at an alpha of 0.05. Analysis was performed on an intention-to-treat basis for the primary and key secondary outcomes. Key secondary outcomes included: 30-day survival free of pharmacologic or mechanical cardiac support, neurologic recovery at any point within the first 30 days, and major bleeding events. Pre-specified post-hoc subgroups included age (</>65 years), sex, location of OHCA, initial rhythm, pH (above or below median), lactate (above or below median), and cause of arrest. The data safety monitoring board reviewed the study every six months or incrementally after 30 patients had been enrolled since the last review, whichever came first. Termination criteria included pre-specified stopping rules for futility based on the test statistic and number of patients enrolled.

4345 patients with OHCA in the Prague EMS service area were assessed for eligibility. 264 patients were randomised, of which eight patients were subsequently excluded (mostly due to refusal of consent from patient/family). 124 patients were randomised to the hyperinvasive intervention arm, and 132 to the control. These 256 patients comprised the population in the primary analysis. Most patients were excluded due to death prior to randomisation (1601), ROSC prior to randomisation (1263), or unwitnessed arrest (677).
The median age of patients in the intervention and control arms was 59 and 57, respectively, and 82/83% were men. The pre-arrest burden of comorbidities was roughly

equal: 44/51% had hypertension, 18/21% had diabetes, and 16/21% had coronary artery disease. A plurality of arrests occurred in a public place (36 and 41% of patients, respectively); however, roughly 15% of arrests were witnessed by EMS. The initial rhythm was ventricular fibrillation in 58% of cases in the hyperinvasive strategy and 64% in the standard care group. About a fifth of patients in each arm presented in asystole, and another fifth in PEA.
Of the patients who were transported to the hospital and had labs drawn, pH and lactate demonstrated increased metabolic derangement in the intervention arm (pH 6.93 vs. 7.03, lactate 12.5 vs. 10.4). The ultimate cause of cardiac arrest was attributed to acute coronary syndrome in about half of patients in each arm, with chronic CAD (11 and 14%), pulmonary embolism (10 and 9%), and chronic heart failure (7 and 5%) filling out the key aetiologies.

11 crossovers occurred from the standard to the invasive strategy, and nine crossovers from invasive to standard. The time from arrest to hospital arrival was 49 minutes in the hyperinvasive bundle strategy, and 60 minutes in the standard care group. 66% of patients allocated to the hyperinvasive strategy were implanted with ECMO.

The primary outcome of survival at 180 days with good neurological function occurred in 31.5% of patients in the intervention group and 22.0% in the control group, RR, 1.63; (95% CI, 0.93 to 2.85), a difference that was not statistically significant. The key secondary outcomes of neurologic recovery at 30 days occurred in 30.6% in the intervention group and 18.2% in the control group, RR 1.99; (95% CI, 1.11 to 3.57), a difference that was statistically significant. Cardiac recovery occurred in 43.5% of patients in the intervention group and 34.1% in the control group, RR 1.49; (95% CI, 0.91 to 2.47). Major bleeding events occurred in 31% of patients in the intervention arm and 15% in the control group.

Critique

The primary outcome of neurologically intact survival at six months was not statistically significant between the hyperinvasive intervention arm and the standard care arm; the odds ratio was 1.63 with a lower bound that crossed one at 0.93. The authors must be commended for undertaking the largest randomized controlled trial to date studying ECMO in out of hospital cardiac arrest. Enrolling 256 patients in a study with such complex interventions and so little time to implement them is no small feat. However, the study was powered to detect an absolute difference of 15% with 90% power, which while not either mechanistically or retrospectively unreasonable, is ambitious. The absolute difference between the invasive strategy and standard strategy was 9.5% in this population, which if is to be believed, likely still reflects a clinically important improvement in a patient-oriented outcome. ECMO, and other associated interventions

in the hyperinvasive arm, are systemically costly and resource intensive; while beyond the scope of either the paper or this critique, there is likely some economic break-even point factoring in the cost of delivering this therapy with the gain in quality-adjusted-life years. It is difficult to imagine that an absolute difference of 9.5% would be insufficient by this alternative, systems-level view of clinical importance.[2,3]

Throughout this review, we have attempted to be particular in how we refer to the two groups in the study. For the intervention group, we use descriptors such as “invasive”, “hyperinvasive”, and/or “bundle”. It is easy at first glance to conclude that this is a study comparing ECLS (i.e.: veno-arterial extracorporeal membrane oxygenation support during active CPR) with standard care. This is not how the study was (at least initially) designed and is a problematically simplistic way of interpreting the results. Patients allocated to the intervention arm were to receive a group of interventions, each component of which with a putatively different mechanism. The intervention arm, as designed, consisted of at least five severable actions: early intra-arrest transport, pre-hospital therapeutic hypothermia, mechanical chest compressions, ECLS, and early invasive angiography. For reasons that will be discussed subsequently, the knowledge gleaned from the trial as published today is functionally a treatise on peri-arrest ECMO. Though ECMO was a component of the intervention arm, and reasonable minds may disagree about how central ECMO was to the benefit hoped for in the original study design, ECMO was intended to be one element of an aggressive, hyperinvasive, style of cardiac arrest resuscitation. Consequently, the implementation of ECMO here is different than what one may expect if this were a trial strictly comparing ECLS to standard care.

82 of 124 patients allocated to the invasive strategy received ECLS. This means one-third of patients in the intervention arm never received ECMO. This discrepancy is almost fully attributable to the study design; because the initial bundle of interventions looked at mechanical chest compressions to facilitate safer and more effective early intra-arrest transport to the hospital, randomization had to occur on scene. 26 minutes elapsed between randomization and hospital arrival, where the interventional cardiology team was waiting and logistically able to cannulate patients for a pump run. Twenty-six minutes comprises almost half of the code time attended by healthcare professionals, and unsurprisingly, 34 patients (27%) randomized to the intervention arm attained stable ROSC before hospital arrival. By virtue of early intra-arrest transport being one of the bundle components, the standard care group did not receive protocolised early transport. Prehospital termination of resuscitation was allowed in the standard care group but not in the intervention group (34% vs. 1%, respectively). Because of this and other differences, there is no direct control group (without secondary analyses) available

to attempt to disentangle the true effect of ECMO from the larger population of all randomized patients in the intervention arm.

It is interesting to note that in the intervention arm, patients could receive ECLS for either refractory cardiac arrest with CPR in progress or ongoing cardiogenic shock post-ROSC (defined as “sustained hypotension below 90 mm Hg” systolic or need for “moderate to high doses of vasopressors”). This is not an unusual choice in ECPR studies; Yannopoulos’ ARREST trial used similar criteria for cannulation.[4] The Prague OHCA Study does not report the split between cannulating for refractory arrest versus shock. However, the median door-to-cannulation time was 12 minutes, with an interquartile range of 9-15 minutes. As three-quarters of patients were cannulated within 15 minutes of catheterisation lab arrival, available evidence suggests that all patients cannulated were likely peri-arrest and exhibited florid haemodynamic instability. ECMO implantation, when offered, occurred quickly and in direct response to cardiac arrest or its immediate sequelae, not delayed haemodynamic decompensation hours after ROSC in the ICU. Still, it is interesting to speculate whether there is a difference in outcome cannulating the refractory arrest versus the refractory shock patient, or whether the two states exist so close on a continuum of haemodynamic collapse to be indistinguishable. This could represent a source of heterogeneity within the intervention arm. Is there positive prognostic value in achieving organized electrical and mechanical activity, even if insufficient to sustain an acceptable MAP for long? Intermittent ROSC was noted in a third of all patients.

More concerning is the issue of crossovers. 20 patients received a different treatment than what they were allocated to—7.6% of the study population. Nine patients crossed over from the intervention group to the control group, due to perceived futility of further invasive interventions. Zero of these nine patients survived. It would have been preferable to exclude these patients prior to enrolment, and in fact, 29 patients were screened but excluded due to physician decision not to enrol. However, by nature of the study design, enrolment occurred on scene, and the cannulating proceduralist was not able to assess the patient for inclusion/exclusion criteria until hospital arrival. Crossovers were handled on an intention-to-treat basis for the primary analysis, so patients were analysed in the group they were initially assigned to, irrespective of treatment received. There were nine patients in the hyperinvasive intervention group, all of whom died, who were never exposed to the potentially beneficial treatment.

11 patients crossed over from the standard care arm to the treatment arm, at the discretion of the treating physician on scene and after two additional unsuccessful defibrillations post-randomization (which is unintuitive given the study was not restricted to patients with VT/VF, and one patient that crossed over was in a non-

shockable rhythm). Among these 11 patients, one achieved ROSC during transport and the remaining ten were placed on ECMO. 4 of 10 reached the primary outcome of six-month neurologically intact survival. [The lone patient that achieved stable ROSC prior to cath lab arrival survived neurologically intact.] As a reminder, the statistics of the study as reported are an absolute difference of 9.5% and RR, 1.63; (95% CI, 0.93 to 2.85), for a trend that approaches but does not reach statistical significance, with a frequentist p-value of 0.09. If the ten cannulated control-to-intervention crossovers are handled on an as-treated basis, the primary outcome changes to survival in 43/134 (32.1%) in the intervention group and 25/122 (20.5%) in the control group. At the same alpha of 0.05 and 90% power, this is an absolute difference of 11.6%, with a p-value of 0.047 and a fragility index of 1. The study now shows statistically significant benefit in the intervention arm.

Perhaps it is not fair to fully embrace the preceding, rudimentary, as-treated analysis. There is likely strong selection bias in which patients were crossed over. We note that 14 of 20 crossovers occurred in the first quarter of patients enrolled (if patient numbers were assigned sequentially), and crossovers were sharply curbed as the study progressed, perhaps reflective of changing local practice patterns. Nevertheless, it is unclear why any crossover from the standard to the intervention arm should be allowed in a study of a last-ditch salvage therapy in refractory cardiac arrest. The purpose of this randomized controlled trial is to assess whether salvage therapy works as assessed by mortality. There is no way of knowing whether standard treatment would have failed had the patient not been crossed over, especially given the striking time-to-pump similarities between the crossover and randomized populations (median 62 vs. 61 minutes), indicating that crossovers did not experience prolonged resuscitation and were not a super-refractory subset of the standard care population.

A post-hoc analysis was performed looking at all patients treated with ECLS, irrespective of allocation. 4 of 10 (40%) and 16 of 82 (20%) reached the primary outcome in the crossover and allocated population, resulting in pooled neurologically intact survival of 22%. There is no appropriate control group to contextualize these results in the original publication. However, a secondary analysis published separately by the study authors in Critical Care addresses this question.[1] (28). Evaluating patients who did not achieve prehospital ROSC (so approximating randomization for ECMO at the time of hospital arrival), survival was 1 of 81 (1.2%) in the standard ACLS group and 22 of 92 (23.9%) in the ECLS group. A multivariable Cox proportional hazard ratio correcting for age, sex, initial rhythm, PCI, and arrest length estimates a hazard ratio of 0.21 for death at six months with ECLS treatment (95% CI, 0.14 to 0.31, $p < 0.001$). In young (<65 years) patients with witnessed cardiac arrest and transport to the referral catheterisation lab in under 60 minutes of total code time, ECLS is not futile.

The Prague OHCA Study was conducted between March 2013 and October 2020, spanning approximately 7.5 years. Resuscitation and critical care management changed significantly in that near decade. The intervention arm originally featured a bundle of five actions: early intra-arrest transport, mechanical chest compressions, intra-arrest therapeutic hypothermia, ECLS, and early invasive angiography. The LUCAS mechanical chest compression was made available to patients in either arm after the publication of the major LINC RCT in 2014 showing no mortality difference between mechanical and manual chest compressions.[5] 92 and 79% of patients in the intervention and standard care group received mechanical chest compressions; there is inadequate separation in exposure to this intervention for this study to test the effect of mechanical chest compressions (nor is there a clinical need, given interim publications answering this question). With the availability of mechanical chest compression devices, intra-arrest transport with CPR in progress was more feasible for the standard care group. 15 protocol deviations of intra-arrest transport with CPR in progress were reported out of the 121 patients in the standard care group, blurring the effect of early intra-arrest transport on the primary outcome. Recent retrospective work suggests routine intra-arrest transport may be harmful.[6–8]

Early therapeutic hypothermia was to be initiated with the RhinoChill transnasal evaporative cooling device in the intervention arm. 17% of patients in the intervention arm were exposed to this treatment (and 9% in the control group) before the RhinoChill was pulled from clinical availability in 2016. The 2019 PRINCESS trial[9] examining intra-arrest RhinoChill found a non-significant difference in neurologically intact survival in a study of 677 patients (16.6% vs 13.5%, RR, 1.23; (95% CI, 0.86 to 1.72)). Even if intra-arrest cooling may be beneficial, the small proportion of patients exposed and the interim publication of a larger RCT makes any information added from the Prague OHCA Study of marginal importance, at best. Similarly, both groups were to receive TTM in-hospital to 33 degrees C. The interim publication of the TTM trial[10] in 2013, which failed to show benefit for cooling to 33 degrees, caused a change in protocol in the Prague OHCA Study to allow hypothermia or normothermia; 95% and 70% of patients received TTM in the intervention and control arms. Finally, early invasive angiography was performed in 98% of patients of allocated to the intervention arm. Early angiography was only indicated in the setting of traditional criteria (i.e.: ST elevation) in the control group. Interim high-quality publications have shown no benefit to routine, emergent post-cardiac arrest angiography (versus delayed angiography), somewhat obviating the equipoise that did exist on this front at the trial outset.[11,12]

Given the leaps in our understanding of cardiac arrest resuscitation science from over the prior decade, the trial evolved as new evidence emerged. Of the five-intervention bundle that comprised an aggressive style of resuscitation in 2011, only ECLS emerges in

2022 as the intervention that was both consistently studied throughout the trial and that has remaining clinical equipoise. The other impact of a 7.5 yearlong trial is on the development of institutional expertise. ECMO is not a new concept. The ELSO Red Book was in its fourth edition in 2012, but the concept of ECPR was still novel in the early 2010s. [The ELSO ECPR textbook was not published until a first edition in 2021.] We know from other areas of medicine that there is strong operator- and hospital-volume dependent associations with mortality in the treatment of complex patients, from complex hepatopancreatobiliary surgery[13] to neurointerventional thrombectomy for stroke.[14] Though there is some evidence that suggests a volume-outcome trend may not be as robust in adult ECMO patients[15,16] compared to paediatric patients,[17,18] a wealth of institutional knowledge and inertia can develop in 7.5 years, potentially mediated by turnover of involved healthcare professionals. It is interesting to speculate whether mortality or morbidity changed chronologically, as this single referral medical centre in Prague accumulated volume and experience managing complications.

Initial electrocardiographic rhythm was not a criterion for patient selection in this trial. Approximately 60% of patients were in ventricular fibrillation, but the remaining 40% were split evenly between PEA and asystole. A hypothesis generating post-hoc analysis unsurprisingly demonstrated marked differences in survival between shockable and nonshockable rhythms. 35 of 72 (48.6%) patients initially in VF in the intervention arm survived, compared to 4 of 52 (7.7%) in PEA/asystole. Given the cost, broadly defined, of ECLS, it may be reasonable to restrict access in current clinical practice to patients with an initially shockable rhythm. While survival was relatively poor in nonshockable patients, it was not dismal, in the sense of <1% survival used to craft termination of resuscitation guidelines (7). Future work may further delineate a subset of patients who present in asystole or PEA but who may benefit from ECLS, especially given the even worse survival of these patients who did not receive hyperinvasive care (1 of 48, 2.1%). Despite all patients having a witnessed arrest and EMS arriving nine minutes later, 40% of patients had a non-shockable rhythm (in a trial where >70% of all patients were retrospectively confirmed to have a cardiac aetiology of arrest). This concords with in-hospital arrest data that suggests non-shockable initial rhythms are common even in cardiac causes of arrest (8), and casts doubt on using initial rhythm as a sole or major determinant in establishing a differential of potentially reversible causes.

The Prague metropolitan area encompasses 1.25 million people and attends 500 to 600 cardiac arrests per year. The rate of bystander CPR was quite high at 98-99%, which may not be widely translatable beyond the studied area, given an average rate of bystander CPR of 58% with wide variability in EuReCa TWO.[19] A physician responds via fly car to cardiac arrests in the Prague EMS system and leads the resuscitation. Physician response

is less common in many parts of the world and has been associated with better outcomes.[20]

We finally note an interesting peculiarity in the primary and secondary data relating to neurologically intact survival. 38 patients in the hyperinvasive group had CPC 1 or 2 at 30 days post-arrest; that number increased to 39 patients (+1) at 180 days. Similarly, five more patients regained normal neurologic function between one and six months in the standard care group. Outcomes assessment was performed by a blinded neurologist, and inter-rater reliability is substantial for the CPC with a kappa of 0.70.[21] Recovery from a complex, systemic insult such as cardiac arrest with prolonged resuscitation takes time, and discretion must be exercised to prevent premature withdrawal of care. All patients received neuroprognostication and decisions relating to de-escalation of care in accordance with contemporaneous international guidelines. However, six patients saw an improvement in neurological function more than a month after injury; the ARREST trial reported a median ICU length of stay of 21.5 days in survivors.[4] In light of renewed interest in preventing premature withdrawal of life support therapies,[22,23] this protracted clinical recovery seen in ~10% of all patients with good outcome merits further thought about prognostication and delayed waking/recovery in this population.

Body of Evidence

The only other major RCT of ECPR at the time of this publication was the ARREST trial, published in The Lancet in 2020.[4] ARREST was a single-centre, phase 2 trial conducted in Minneapolis, Minnesota, USA, and was stopped for superiority at the recommendation of the DSMB after 30 patients were enrolled. The ARREST trial demonstrated exceptional outcomes—1 of 15 patients (7%) survived to hospital discharge in the standard care arm and 6 of 14 patients (43%) in the intervention arm. ARREST looked at the effect of ECPR more centrally as other adjunctive therapies were not studied and patients were enrolled upon hospital arrival. Though the (catheterisation lab) door-to-pump time was faster in ARREST (7 vs. 12 minutes), the overall time-to-ECLS was similar (59 vs. 61 minutes). Despite the many similarities between the studies, ARREST ultimately cannulated 12 patients (~7.5x fewer patients than the Prague OHCA Study), enrolled patients up to 75 years old, and only included patients with an initial shockable rhythm. A subgroup analysis of shockable rhythm outcomes in the Prague OHCA Study estimates an absolute benefit size of 15.3% (95% CI, 0.0 to 30.6%). Accounting for higher-than-expected survival in the standard care group (33.3%) due to the earlier randomisation and more liberal definition of refractoriness, the outcomes in these two trials appear roughly congruent.

Since the publication of the Prague OHCA Study, the INCEPTION trial[24] in the Netherlands randomised 134 patients to either ECPR or standard care (24). 30-day

neurologically favourable survival was numerically similar between the groups, at 14/70 (20%) in the ECPR group and 10/64 (16%) in the standard care group, RR, 1.4; (95% CI, 0.5 to 3.2). The door-to-pump times were longer in INCEPTION at 20 minutes, leading to approximately a 15-minute increase in total code time prior to ECMO support (median 74 minutes). Like the Prague OHCA Study, randomisation occurred prior to hospital arrival, and not all patients in the ECPR group received the treatment.

A recent systematic review and meta-analysis of ECPR estimates neurologically intact survival of 18%.[25] This is lower than both ARREST and the Prague OHCA Study, which may point to differences in patient selection criteria, systems of care, or operator experience.

Should we offer a bundle of treatment that includes early intra-arrest transport, ECMO, and coronary angiography to otherwise healthy patients in refractory, witnessed, out-of-hospital cardiac arrest?

Maybe. In a highly selected patient population and in the hands of a skilled system, ECMO is a reasonable option to treat refractory cardiac arrest.

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EMERGE

Hauw-Berlemont C, Lamhaut L, Diehl JL, Andreotti C, Varenne O, Leroux P, et al. Emergency vs Delayed Coronary Angiogram in Survivors of Out-of-Hospital Cardiac Arrest: Results of the Randomized, Multicentric EMERGE trial. JAMA Cardiol 2022;7(7):700-707

Introduction

Out-of-hospital cardiac arrest (OHCA) is a medical condition that carries significant health risks, leading to a high rate of morbidity and mortality. In fact, only around 9% of patients in the UK^1 manage to survive until their hospital discharge.[1] When OHCA is caused by ST elevation myocardial infarction, the advised course of action is fairly straightforward: primary percutaneous intervention (PCI) should be administered once spontaneous circulation has resumed.[2]

However, if the OHCA is not accompanied by ST elevation on an ECG, the protocol for immediate coronary angiography (CAG) and PCI becomes less clear. The current guidelines recommend tailoring the treatment to the individual patient, taking into consideration the specifics of the OHCA situation and any pre-existing health conditions. In situations where a non-ST elevation myocardial infarction might be the cause of the OHCA, and the possibility of a non-coronary cause for the cardiac arrest is low, urgent CAG is endorsed by both the European Society of Cardiology[2] and the Resuscitation Council UK.[3]

Despite these guidelines, recent evidence,[4–6] albeit restricted by selective and underpowered study groups, has suggested that immediate CAG may not actually provide any benefits for patients who have been resuscitated after experiencing OHCA without ST elevation on their ECG. Amid this relative therapeutic uncertainty, the EMERGE trial has been initiated. This trial aims to contribute further data from randomised controlled trials in order to definitively answer this clinical question.

Synopsis

The EMERGE trial aimed to evaluate the 180-day survival rate of patients who had experienced an out-of-hospital cardiac arrest (OHCA) without ST segment elevation on their post-resuscitation ECG. The trial considered only patients without an apparent non-cardiac cause of arrest. Two groups of patients were compared: one that underwent emergency coronary angiography (CAG) and another that had delayed CAG.

The trial was a multicentre, randomised, open-label study conducted nationwide. Survivors of OHCA were randomly assigned, in equal proportions, to either emergency CAG or delayed CAG, with the latter procedure being performed within 48-96 hours. The trial included participants from 22 centres across France, with data collection taking place from January 2017 to November 2020. The results were published in the Journal of the American Medical Association for Cardiology in July 2022.

The trial incorporated patients aged 18 or over who had experienced an OHCA with return of spontaneous circulation (ROSC), without a clear non-cardiac cause of arrest, and who had been admitted to a centre equipped with both an intensive care unit and a round-the-clock interventional cardiology service. The exclusion criteria were comprehensive, omitting patients under 18 years old, those with in-hospital cardiac arrest or without ROSC, patients who showed ST segment elevation on their post-resuscitation ECG or a suspected non-cardiac aetiology, and those with comorbidities reducing life expectancy to less than a year. Additionally, pregnant individuals, adults under legal guardianship, and participants in another interventional trial were excluded.
An interesting element of the study was that investigators could perform a CAG sooner than 48-96 hours in the delayed group if certain conditions emerged, such as new ST segment elevation or left bundle branch block on the ECG, shock unresponsive to inotropes, electrical storm, or new segmental hypokinesia/akinesia on echocardiogram.

The trial used electronic randomisation, with a centralised system. The previously published trial design[7] stated that each participant would be assigned a randomisation number, and a pre-programmed randomisation list would be created by the study statistician, using a mix of small blocks of various sizes. This list was to be generated and reviewed by an independent statistician, not associated with the study.

The primary outcome of the study was to measure the 180-day survival rate without significant neurological effects, assessed by an independent physician blinded to randomisation and using the Cerebral Performance Category 1 or 2. Secondary outcomes included shock, tachycardia, and episodes of atrial fibrillation within the first 48 hours after hospital admission, changes in left ventricular ejection fraction from baseline to 180 days (measured by echocardiogram), severe neurological effects (defined by Cerebral Performance Category 3 or 4 and assessed at discharge from the intensive care unit, after 90 days, and after 180 days), overall mortality and the duration of hospital stay.

Drawing upon data from the Parisian Region Out of Hospital Cardiac Arrest (PROCAT) study[8]^8, the researchers predicted a primary outcome in the control group of 36%. They proposed a hypothesis of a 10% absolute difference between the intervention and

control groups. In order to ensure the study had sufficient power (80% power at a 5% significance level), a total of 678 patients were required. However, the investigators planned to recruit 970 patients to account for a potential 10% loss to follow-up and a possible crossover rate of 30%. The intention was to perform the analysis on an intention-to-treat basis.

Throughout the trial period, 338 patients were screened, and 59 of these were excluded. Consequently, a total of 279 patients were enrolled in the study from January 2017 to November 2020. Out of these, 141 patients were assigned to the emergency coronary angiography (CAG) group, while 138 patients were placed in the delayed CAG group. However, due to pre-specified rules related to the rate of patient inclusion, the funding was terminated before the enrolment objective was achieved.

Demographics at the baseline stage were well balanced. The emergency and delayed CAG groups had comparable average ages and were predominantly male, with men constituting 77.3% of the emergency CAG group and 66.7% of the delayed CAG group. The majority of out-of-hospital cardiac arrest (OHCA) events were witnessed (88.7% in the emergency CAG group and 92.7% in the delayed CAG group), and immediate CPR was provided by bystanders. The median time from OHCA to the provision of basic life support was 3 minutes (interquartile range 1-6 minutes) in the emergency CAG group and 2 minutes (interquartile range 1-5 minutes) in the delayed CAG group. The initial rhythm of the cardiac arrest was non-shockable in both groups (65.2% in the emergency CAG group and 69.9% in the delayed CAG group).

In the emergency CAG group, 126 out of 141 (89.4%) patients underwent the procedure. Of the 15 patients who did not undergo the procedure, 7 had passed away, while the rest did not have a specified reason for not undergoing CAG. In the delayed CAG group, only 74 out of 138 (53.6%) patients underwent the procedure. Of the 64 patients who did not undergo the procedure, 40 had died, 13 had severe brain damage, 8 were haemodynamically unstable, and the remaining 3 had no specified reason for not undergoing CAG. The average time delay between randomisation and CAG was 0.6 hours in the emergency CAG group, compared to 55.1 hours in the delayed CAG group.

Regarding the primary outcome, there was no significant difference between the two groups. The 180-day survival rate with a Cerebral Performance Score (CPC) of 1 or 2 was 34.1% (47 out of 141) in the emergency CAG group and 30.7% (42 out of 138) in the delayed CAG group, resulting in a hazard ratio of 0.87 [95% confidence interval 0.65-1.15, with p= 0.32]. Moreover, no difference was observed between the two groups in any of the secondary outcomes.

Critique

The EMERGE trial boasted numerous strengths. It was a multicentre trial that included patients from 22 centres across France, and the patients' characteristics in the two groups were suitably similar.

The primary outcome of the study was well defined and relevant. The significance of including a favourable neurological outcome as an endpoint, alongside survival, has been increasingly emphasised following the publication of key trials like PARAMEDIC2.[9]. In this trial, the use of adrenaline in Advanced Life Support was linked to a significant primary outcome of improved overall survival, as well as a significant secondary outcome of survival with severe neurological impairment. In the EMERGE trial, neurological outcome was included in the primary outcome, and the degree of neurological impairment was assessed independently of the study by a clinician who was blinded to the process, using a validated assessment tool (Cerebral Performance Category).

Given the specific inclusion criteria of adult patients who had experienced an out-of-hospital cardiac arrest (OHCA) with return of spontaneous circulation (ROSC), with no apparent non-cardiac cause of arrest and without ST elevation on a post-resuscitation ECG, it's understandable that patient recruitment was slow. Recruitment was further complicated initially by the requirement for signed consent by proxies present at the site of cardiac arrest. Out of 338 patients, 37 were excluded due to the absence of informed consent. However, this consent requirement was later modified in September 2019.

The principal limitation of the trial was that it was significantly underpowered due to difficulties with patient recruitment. Before the study commenced, the power calculation suggested that 678 patients were needed to identify a statistically significant difference between the intervention and control groups. However, only 279 patients were assigned to a study group before the funding was terminated. Thus, it's unsurprising that there was no difference between the two study groups in terms of both primary and secondary outcomes.

The study investigators attempted to mitigate this issue by conducting a meta-analysis. This involved pooling patient populations from historical trials with similar methods[4–6] that compared early versus delayed CAG with the contemporary EMERGE data. While this significantly increased the patient population to 1446 patients, the pooled findings corroborated the original EMERGE trial results, indicating no benefit from early CAG.

Another significant point is that only 51 out of the 138 patients assigned to the delayed CAG group received the defined intervention, while an additional 23 patients underwent CAG before 48 hours. Crucially, as per the intention to treat analysis, these patients were

still included in the final analysis of the delayed CAG group. As a result, 23 out of the 74 patients who underwent CAG in the delayed CAG group did not actually have a delayed CAG. The criteria for cross-over were predefined (new ST-segment elevation or left bundle branch block on the ECG, shock unresponsive to inotropes, electrical storm, or new segmental hypokinesia/akinesia on echocardiogram). However, this group likely consisted of patients with probable cardiac pathology who would benefit from CAG, contrasting with the undifferentiated population in the immediate CAG group. This may be another reason why there was no difference in the primary outcome between the two study groups.

Body of Evidence

There's a limited amount of evidence currently available regarding the role of immediate versus delayed CAG following an out-of-hospital cardiac arrest (OHCA) when there's no ST-elevation on the post-resuscitation ECG.

The PROCAT trial[8] is a case in point. It recruited 435 patients with OHCA from a single tertiary centre in Paris between 2003 and 2008, with no clear extra-cardiac cause of arrest. Immediately following resuscitation, they underwent CAG. However, the trial didn't provide a clear definition of the time-frame between study recruitment and CAG. In this cohort, 301 patients showed no ST elevation on their post-resuscitation ECG, yet, 58% (176/301) were found to have at least one significant lesion on coronary angiography.

The PROCAT trial didn't include a control group, making it impossible to evaluate the impact of immediate CAG as an intervention. The overall hospital survival of the 435 patients who underwent an immediate coronary angiography was 39%. However, it was observed that the survival rate was significantly higher in patients who had successful PCI following angiography, rather than no or failed PCI. This elevated survival rate persisted even in the subgroup of patients with no evidence of ST elevation on their post-resuscitation ECG.

A 2012 study by Bro-Jeppesen et al,[10] however, didn't find any survival advantage when emergency CAG was performed on the patient subgroup with no ST elevation on their post resuscitation ECG. Neither attempted nor successful PCI was identified as an independent predictor of survival in this patient subgroup.

However, the Bro-Jeppesen[10] study had limitations, and was susceptible to selection bias. 592 resuscitated OHCA patients were recruited from a single centre in Copenhagen, but 113 were excluded for presumed non-cardiac cause of arrest. Any patients with a Glasgow Coma Score (GCS) of 9 or above were also excluded, though the

reasons for this were unclear. The decision to proceed to emergency CAG was solely at the discretion of the treating clinician, and was neither randomised nor controlled. Therefore, the study's susceptibility to significant selection bias must be considered when interpreting the trial results.

More recent randomised controlled trials like TOMAHAWK,[4] COACT,[6] and PEARL[5] have all failed to show any survival benefit from implementing an immediate (versus delayed) CAG strategy in resuscitated OHCA patients with no ST elevation on ECG.

The multicentre TOMAHAWK trial compared an immediate CAG strategy to an initial intensive care evaluation that included delayed or selective CAG, with a primary endpoint of 30-day all-cause mortality. Resuscitated OHCA patients aged above 30 with no ST segment elevation on their ECG were eligible for trial inclusion. The immediate CAG group were transferred to the catheterisation laboratory as soon as possible after hospital admission, whereas the delayed CAG group were first admitted to the Intensive Care Unit (ICU) for further evaluation. Delayed CAG could be performed after a minimum delay of 24 hours at the discretion of the treating physician.

The COACT trial, similar to the TOMAHAWK trial, was an open-label multicentre trial. However, the understanding of delayed CAG in this trial was different from others. Here, angiography only occurred after 'neurological recovery', generally after discharge from the ICU, although the term 'neurological recovery' wasn't clearly defined in this trial. It's worth noting that the COACT trial had the fewest patient crossover events from delayed to immediate CAG. Nevertheless, there was no significant difference in either the primary outcome of 90 day survival or the secondary outcome of 90 day survival with good cerebral performance.

Lastly, the PEARL trial was an international multicentre prospective randomised trial that compared early CAG (within 120 minutes of arrival) versus no early CAG (no CAG within 6 hours of hospital arrival) in comatose adult patients post resuscitation from OHCA. Despite utilising a composite primary endpoint strategy (including multiple measures of efficacy and safety), the investigators did not find a significant difference between the two groups. However, the trial was significantly underpowered. Fewer than half of the 226 patients required via power calculation to be necessary to detect a 17% expected difference between the two trial groups were ultimately recruited.

Should we routinely undertake emergency CAG in resuscitated OHCA patients with no ST elevation on their post-resuscitation ECG?

There is now consistent evidence provided by multiple high-quality randomised controlled trials that emergency CAG does not provide a survival benefit over delayed or selective CAG.

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BOX Trial – Fever Prevention

Kjaergaard J, Møller JE, Schmidt H, Grand J, Mølstrøm S, Borregaard B, et al. Blood-Pressure Targets in Comatose Survivors of Cardiac Arrest. N Engl J Med. 2022 Oct 20;387(16):1456-1466

Introduction

The optimal temperature management strategy following successfully resuscitated cardiac arrest with persistent coma is an area of significant controversy. In two landmark trials published in 2002, the efficacy of early therapeutic hypothermia (32-34°C) for 12-24 hours emerged. However, successive, larger, and better-designed trials have refuted these findings. Thus, the accumulating evidence suggests a normothermia strategy with an emphasis on fever prevention. However, the basis for this latter component is largely empirical.

The overall temperature management strategy encompasses: the rate of cooling, or warming, to the initial target; the target temperature itself; the duration of this first phase; the rate of rewarming to the next phase of fever prevention; the threshold for, and the nature of, the intervention; and the duration of fever prevention. Simultaneously, the sedation strategy; planned trials of and response to awakening; together with the management of signs of catastrophic hypoxic-ischaemic encephalopathy, all influence outcome and confound clinical trials.

Protracted and complex intervention algorithms are burdensome to patients, their families, and caregivers. If they are not of benefit, then we are obligated to stop delivering them.

Synopsis

This trial set out to determine if 12 or 36 hours of an actively maintained core temperature of 37.0°C, following 24 hours of actively maintained 36.0°C, improved the outcome following out-of-hospital, presumed cardiogenic, cardiac arrest. Temperature control was delivered either by specialist surface or intravenous device. The intervention was terminated if the patient awoke.

This trial was a substudy encompassed within the 2x2 factorial Blood Pressure and Oxygenation Targets in Post Resuscitation Care (BOX) trial.[1,2] Patients at two Danish

cardiac arrest centres were further randomised in a 1:1 ratio, to one or other duration of post-rewarming normothermia. There was no blinding to allocation.
Patients were enrolled if they were 18 years of age or older; they had suffered an out-of-hospital cardiac arrest of presumed cardiac cause; had a return of spontaneous circulation (RoSC) for at least 20 minutes following resuscitation; and had a Glasgow coma score of <8 at the time of hospital admission. Exclusion criteria were essentially the antithesis of the inclusion with the addition of a known life-limiting illness or severe chronic neurodisability.

Recruitment took place over a nearly 5-year period (March 2017 – December 2021) and was affected by the COVID-19 pandemic (from January 2020).

The primary outcome was a composite of death (from any cause) or survival with a cerebral performance category (CPC) of 3 or 4 at hospital discharge within 90 days. There were multiple secondary outcomes including 90-day Montreal Cognitive Assessment and modified Rankin scale scores.

The power calculation determined that the sample size should detect a 27.5% relative difference in the primary outcome with 80% power at the 5% significance level. The pre-specified statistical analysis used a Cox proportional-hazards methodology with adjustment for site. Subgroup analyses were defined a priori to consider the effects of sex, age, chronic obstructive pulmonary disease, chronic renal impairment, chronic hypertension, rhythm during cardiac arrest, and evidence of ST-elevation on the post-arrest 12-lead ECG.

A total of 1196 patients were assessed for eligibility, of whom 1008 fulfilled the inclusion criteria. Of these, 802 were randomised with the remainder excluded. 401 patients were allocated to each of the duration groups. 13 patients declined to consent. This resulted in 393 patients in the 12-hour intervention arm, and 396 in the 36-hour arm. 90-day assessments were completed on 253 and 252 patients respectively, with 132 and 140 patients respectively dying prior to this time point.

The two groups were very well matched at baseline. The patient cohort had a median age of 62 and was 80% male. 85% had a witnessed arrest. 88% received bystander CPR. 85% had a shockable rhythm during their arrest. The mean time to RoSC was 21±14 minutes. 45% had ST-elevation, 92% underwent immediate coronary angiography and 47% underwent a percutaneous intervention.

The median temperature at randomisation was 35.5°C. In the first 72 hours, 50% of patients in the short duration group had a temperature recorded of >37.7°C, compared

to 38% of patients in the longer duration group. In the same time period, a temperature >38.5°C was recorded in 12% of the short duration group and 6% of the long duration group.

Death from any cause or a CPC of 3 or 4 at hospital discharge within 90 days occurred in 127 of 393 patients (32.3%) in the 36-hour group and 133 of 396 patients (33.6%) in the 72-hour group (hazard ratio, 0.99; 95% CI, 0.77 to 1.26; P = 0.70). Of these, 116 (29.5%) and 120 (30.3%) had died. Among survivors, the median CPC at 90 days was 1 (1-5). These results were consistent across all subgroups and no interaction with blood pressure or oxygenation target interventions was found. The median Montreal Cognitive Assessment score among patients alive at 90 days was 26 (24–29) and 27 (24–28) respectively. The median modified Rankin scale scores were 1 (0-6) in both groups. There were no significant differences in the prevalence of any of the pre-specified adverse events.

Critique

This trial was well designed and performed in two centres of excellence with a proven track record of clinical trials in this area. This is borne out by the detailed protocol, the very high levels of immediate cardiac interventions, and a near 70% survival with CPC 1.

This study has some limitations. As a substudy of a 2x2 factorial trial with an unblinded intervention, there is a risk of a type II (false negative) error. However, a significant level of mitigation against this was included in the design.

The fact that a significant minority of patients in both groups had a temperature over 37.7°C in the study period may have masked any effect of fever prevention on outcomes. There will be concerns about the generalisability given the setting and good early prognostic factors in the selected patient cohort.

Body of Evidence

Two separate systematic reviews and meta-analyses of targeted temperature management (TTM) following adult cardiac arrest were published in 2021.[3,4] They both conclude that normothermia, as opposed to hypothermia, should be the target of therapy. The recommended duration is 72 hours based on empirical evidence.
Two studies published since these meta-analyses found no benefit of mild hypothermia to normothermia.[5,6]

In a 2020 provocative review, three opinion leaders make a case for the components of "high-quality TTM" and suggest that "low-quality TTM" has masked the efficacy of this intervention in day-to-day practice and some trials.[7]

A 2021 systematic review and meta-analysis[8] of animal studies in this area concluded that these studies support the efficacy of therapeutic hypothermia. However, the animal models used are not consistent with the human experience.

This is the first study to investigate a shorter duration of normothermia. It found no evidence to support a 72-hour duration over 36. The evidence appears to suggest that any future TTM trials should randomise to effective (high-quality) normothermia at 37.0°C versus no temperature management. Optimal sedation strategy, including daily cessation for neurological assessment, treatment for the underlying cause of the arrest, and best-practice neuroprognostication must all be protocolised.

There is significant evidence to suggest that persistent spontaneous hypothermia in the adult, post-cardiac arrest, population is a reliable sign of catastrophic brain injury. Whether pyrexia is adaptive, maladaptive, or beneficial, neutral or detrimental, may well be a characteristic of the individual patient. Adding repeated measures of the extent and progression of brain injury might be a valuable selection / stratification tool in future TTM trials. However, the optimal and pragmatic method for doing this is uncertain. Serial measurements of neurone-specific enolase, processed EEG parameters during a sedation hold, and pupillometry are viable candidates, probably in combination.

Should we continue to make all efforts to prevent core temperature rising to >37.7°C in the 24 to 72 hour period after cardiac arrest in patients with persistent coma?

Probably not. This trial adds to the growing evidence that no component of targeted temperature management in this patient group improves outcome.

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BOX-BP

Kjaergaard J, Møller JE, Schmidt H, Grand J, Mølstrøm S, Borregaard B et al. Blood-Pressure Targets in Comatose Survivors of Cardiac Arrest. N Engl J Med. 2022 Oct 20;387(16):1456-1466

Introduction

Cardiac arrest is a significant and devastating health problem globally. Every year in the United States, there are approximately 350,000 out-of-hospital cardiac arrests[1] (OHCA) and another 290,000 in-hospital cardiac arrests[2] (IHCA). The survival rate to hospital discharge is roughly 9% for OHCA and 23% for IHCA.[1]

One of the critical challenges in managing cardiac arrest survivors is the post-cardiac arrest syndrome, characterised by the systemic ischaemia/reperfusion response and post-arrest brain injury. A substantial proportion of these patients experience hypotension following return of spontaneous circulation (ROSC), which can exacerbate brain injury and negatively impact outcome.[3] Blood pressure is actively managed as part of most intensive care protocols to deliver sufficient perfusion pressure to the vital organs.[4] A central component of goal-directed post resuscitation care is maintaining adequate perfusion pressure, but evidence for specific blood pressure targets is limited.[5] After a cardiac arrest, patients usually have underlying or concomitant heart disease, so lowering afterload may facilitate cardiac recovery and possibly survival.[6] Vasoactive drugs are used to keep the mean arterial blood pressure above 65 mm Hg in the majority of comatose patients who have been resuscitated after an out-of-hospital cardiac arrest,[7] but vasopressor therapy may have adverse effects. The 2021 European Resuscitation Council and European Society of Intensive Care Medicine guideline on post-resuscitation care[3] advise the avoidance of hypotension (mean arterial pressure < 65 mm Hg) and to achieve a urinary output >0.5 mL/kg/hr, whilst acknowledging these targets may need to be personalised.

Three small randomised trials have compared the efficacy of blood pressure targets with the use of surrogate end points.[8–10] The results of the trials were neutral, and none were powered to evaluate clinical end points and safety. As such, there is a clear need to fill this evidence gap, for a common and highly lethal condition.

Synopsis

The aim of the BOX trial (Blood Pressure and Oxygenation Targets in Post Resuscitation Care) was to evaluate whether a higher (77 mm Hg) or lower (63 mm Hg) target mean arterial blood pressure would be superior in preventing death or severe anoxic brain injury in comatose survivors of out-of-hospital cardiac arrest.

It was an investigator-initiated, dual centre, randomised trial with a 2-by-2 factorial design. Comatose survivors of an out-of-hospital cardiac arrest were randomised to one of two blood pressure targets (blinded) and also to either restrictive or liberal oxygenation (open-label) in the intensive care unit (ICU). Randomisation occurred from March 2017 to December 2021 at two tertiary cardiac arrest centres in Denmark with the use of a web-based system, random permuted blocks of sizes 2, 4, and 6, and stratification according to randomisation site.

Adult patients (≥18 years of age) who had been resuscitated after an out-of-hospital cardiac arrest with a presumed cardiac cause were eligible for inclusion if they had a sustained return of spontaneous circulation (no chest compressions for >20 minutes) and remained comatose (were not able to obey verbal commands) on arrival at the hospital. Specific trial exclusion criteria included unwitnessed asystole and suspected acute intracranial bleeding or stroke.

All patients received temperature control to maintain a temperature of 36°C for 24 hours.[11,12] Patients were invasively mechanically ventilated and were sedated primarily with propofol and fentanyl. Assessment of neurologic outcomes was performed by the attending physician in accordance with guidelines.[3]

No clinical staff, investigators, patients, or outcome assessors were aware of the assigned blood pressure targets. Invasive blood pressure monitoring with a patient-specific blood pressure module (M1006B Invasive Blood Pressure Module, Philips) was used for as long as the patient underwent invasive blood pressure monitoring in the ICU. These modules had been modified for trial use by adjusting the internal calibration to report a blood pressure that was either 10% higher or 10% lower than the actual blood pressure, depending on the assigned blood pressure target.

Thus, by keeping a target of mean arterial blood pressure of 70 mm Hg in all patients, half the patients would have an actual target mean arterial blood pressure of 63 mm Hg (low-target group) and the other half would have a target mean arterial blood pressure of 77 mm Hg (high-target group). Patients were randomised as soon as possible after arrival at the hospital, usually in the ICU and before invasive monitoring was established.

After randomisation, systemic arterial blood pressure was measured with the trial-specific module only.
A three-stage approach for achieving the mean arterial blood pressure of 70 mm Hg was used: firstly, volume resuscitation to a central venous pressure of 10 mm Hg, secondly, noradrenaline infusion, and thirdly, the addition of a dopamine infusion for a maximal dose of 10 µg/kg/min if needed. The total amount of pharmacological circulatory support was quantified as the vasopressor–inotropic score (higher scores indicate a higher degree of support).[13,14]

The primary outcome was a composite of death from any cause or discharge from the hospital with a Cerebral Performance Category (CPC)[15,16] of 3 or 4, indicating severe disability or coma or vegetative state, within 90 days after randomisation (categories range from 1 [no symptoms] to 5 [death]). Secondary outcomes included death from any cause within 90 days, time to renal-replacement therapy, neuron-specific enolase levels at 48 hours after randomisation, the Montreal Cognitive Assessment score[17] at 3 months, the modified Rankin scale score at 3 months, and the CPC at 3 months. [18,19] Scores on the modified Rankin scale range from 0 to 6, with 0 indicating no symptoms, 1 no clinically significant disability, 2 slight disability, 3 moderate disability, 4 moderately severe disability, 5 severe disability, and 6 death. The Montreal Cognitive Assessment tests different types of cognitive abilities and assigns a score between 0 and 30, with a score of 26 or higher being normal. All scoring was undertaken by trained research personnel.

Adverse events were bleeding, infection, arrhythmia, electrolyte or metabolic abnormalities, acute kidney injury with renal-replacement therapy, and seizures.[13] Plasma levels of neuron-specific enolase in patients who were alive at 48 hours were determined by means of electrochemiluminescence (Roche Diagnostics) and with a Cobas analyser system (Roche Diagnostics) in accordance with the manufacturer's instructions.

In a previous study, 6-month mortality among hospitalised comatose patients after resuscitation from an out-of-hospital cardiac arrest was 33%.[20] A sample size of 732 patients would have 80% power to detect a mortality rate of 28% with a two-sided alpha level of 0.05. A total of 800 patients was planned, with follow-up for all patients continuing until 3 months. A two-sided P value of 0.047 was considered significant for the primary outcome, after correction for two planned interim analyses. Statistical analyses were performed with the use of SAS Enterprise statistical software, version 3.8 (SAS Institute).

A total of 802 patients were enrolled in the trial from March 2017 through December 2021. 12 patients withdrew and 1 was erroneously randomised twice, leaving 789 patients, with 393 in the high target group and 396 in the low target group.

The baseline characteristics of the patients were well balanced in the two blood pressure target groups. A typical patient was male (~80%), aged ~63 years, with hypertension (~45%), diabetes (~14%), and a previous myocardial infarction (~22%). ~85% had a shockable rhythm, with a similar number of cardiac arrests being witnessed and bystander cardiopulmonary resuscitation being delivered. ~45% had ST elevation on an ECG and ~91% had coronary angiography, with approximately half this number having percutaneous coronary intervention. The mean duration of cardiac arrest was 21 minutes (SD ~14). The median time from cardiac arrest to randomisation was 146 minutes (IQR, 113 to 187).

Separation of the blood pressure values for the high-target and low-target groups was apparent from the first value measured by the offset blood pressure module, with a mean difference of 10.7 mm Hg between the groups. This difference was maintained up to 48 hours. The mean difference in noradrenaline dose was 0.038 µg/kg/min and the mean difference in vasopressor–inotropic score was 3.5 points.

At 90 days, 133 patients (34%) in the high-target group and 127 patients (32%) in the low-target group had been discharged from the hospital with a CPC score of 3 (severe disability) or 4 (vegetative state), or had died (HR, 1.08; 95% CI, 0.84 to 1.37; P=0.56). Only 24 patients (3%) had been discharged from the hospital with a CPC of 3 or 4: 11 in the high-target group and 13 in the low target group. 31% (122 of 393 patients) in the high-target group and 29% (114 of 396 patients) in the low target group died within 90 days. Renal-replacement therapy was initiated within the first 5 days in 41 patients (10%) in the high-target group and 40 patients (10%) in the low-target group. No significant differences were found in the percentages of patients with adverse events, including infection, arrhythmia, bleeding, and seizure.

The median level of neuron-specific enolase was 18 µg/l (IQR, 11 to 37) in the high-target group and 18 µg/l (IQR, 11 to 34) in the low-target group. Good neurological outcome, defined as a modified Rankin Scale of 0-3, was found in 237 patients (62%) in the high BP target group and 249 patients (64%) in the low target group.

Critique

This double-blind, randomised trial aimed to compare two clinically relevant mean arterial blood pressure targets and their effects on patients who had been resuscitated after an out-of-hospital cardiac arrest. It found no significant difference in the

percentage of patients who died or were discharged from the hospital with a poor neurologic outcome (CPC of 3 or 4) within 90 days. The delicate balance between flow and pressure may be disrupted after an out-of-hospital cardiac arrest, with lower perfusion at a given pressure during the first 12 to 24 hours after the cardiac arrest.[21,22]

The strengths of this trial were that the results were consistent across the objective outcomes (death, neurologic outcomes, and laboratory findings). The sample size was seven times larger than those in previous trials,[9,10] and the double-blinded intervention reduced the risk of bias.

The trial also had limitations. It was conducted in only two high-volume cardiac arrest centres and included a population of patients with a high prevalence of acute coronary syndrome and a relatively good prognosis based on risk factors which may affect the generalisability of the results.

Follow-up in this trial was challenging due to COVID-19 restrictions. As a result, the number of patients available for follow-up visits and assessment of cognitive testing was lower than expected.

The use of dopamine in the trial may surprise some. Dopamine is a catecholamine with inotrope activity, primarily by stimulating α-1, β-1, and dopaminergic receptors. At lower doses, dopamine causes vasodilation in renal, mesenteric, and coronary arteries through its dopaminergic receptor activity. At higher doses, its β-1 receptor activity increases heart rate, stroke volume, and cardiac output. Even higher doses lead to vasoconstriction (via α-1 receptor activity), which increases systemic vascular resistance and blood pressure. Despite these seemingly beneficial effects, dopamine may not be ideal in the critically ill. Firstly, dopamine increases heart rate more than noradrenaline does, which can potentially lead to arrhythmias. Secondly, dopamine may compromise the balance of myocardial oxygen supply-demand, particularly in patients with acute myocardial ischaemia. Thirdly, dopamine may impair the immune response and increase pituitary hormone secretion, including prolactin and growth hormone. In a landmark trial by De Backer in 2010, dopamine was associated with higher mortality and more arrhythmic events compared to noradrenaline in patients with shock. This is particularly relevant as patients post-cardiac arrest can be in a shock state.[23]

Body of Evidence

In a multi-centre, open-label trial of 776 septic shock patients, Asfar compared the effectiveness of targeting a mean arterial pressure of 80-85 mm Hg (high-target group) to 65-70 mm Hg (low-target group) during initial resuscitation.[24] The primary endpoint was mortality at day 28. At this time-point, no significant difference in mortality was

observed between the groups: 36.6% in the high-target group and 34.0% in the low-target group (HR, 1.07; 95% CI, 0.84 to 1.38; P=0.57). Mortality at 90 days was also not significantly different. Serious adverse event occurrences were similar in both groups, but newly diagnosed atrial fibrillation was higher in the high-target group. In patients with chronic hypertension, the high-target group required less renal-replacement therapy, but this was not associated with a difference in mortality. The study concluded that targeting a mean arterial pressure of 80-85 mm Hg, compared to 65-70 mm Hg, did not result in significant differences in mortality at either 28 or 90 days for septic shock patients.

Ameloot and colleagues investigated if an early goal-directed haemodynamic optimisation strategy (EGDHO), with a target mean arterial pressure of 85-100 mm Hg and SvO2 of 65-75%, could improve cerebral oxygenation, reduce anoxic brain injury, and enhance outcomes in post-cardiac arrest patients compared to a mean arterial pressure 65 mm Hg strategy. 112 out-of-hospital cardiac arrest patients were recruited. Although the EGDHO group had a higher mean arterial pressure and cerebral oxygenation during the first 12 hours of their ICU stay ($P < 0.001$ and $P = 0.04$, respectively), there were no significant differences between the groups in the extent of anoxic brain injury or favourable neurological outcomes at 180 days ($P = 0.09$ and $P = 0.96$, respectively). However, serious adverse events were lower in the EGDHO group ($P = 0.02$), leading to the conclusion that targeting a higher mean arterial pressure in post-cardiac arrest patients was safe and improved cerebral oxygenation, but did not improve anoxic brain injury or neurological outcomes.[8]

The COMACARE trial examined the feasibility of targeting low-normal or high-normal mean arterial pressure after out-of-hospital cardiac arrest and its effect on markers of neurological injury. 123 patients were recruited, with 120 included in the final analysis. The primary outcome was neuron-specific enolase concentration at 48 hours after cardiac arrest. There was a clear separation in mean arterial pressure between the groups ($P<0.001$). However, the median neuron-specific enolase concentration at 48 hours was 20.6 µg/L in the low-normal MAP group and 22.0 µg/L in the high-normal MAP group ($P=0.522$), and no significant differences were found in secondary outcomes. The study concluded that targeting a specific range of mean arterial pressures was feasible during post-resuscitation intensive care, but the blood pressure level did not affect neuron-specific enolase concentration at 48 hours after cardiac arrest or any secondary outcomes.[9]

Grand and colleagues undertook a single-centre, double-blind pilot trial to investigate the effect of a higher mean arterial pressure target on biomarkers of organ injury in 50 comatose out-of-hospital cardiac arrest patients. Patients were randomly assigned to a

mean arterial pressure target of 65 mm Hg (MAP65) or 72 mm Hg (MAP72). The primary endpoints were biomarkers of organ injury, including endothelial integrity (soluble thrombomodulin), brain injury (neuron-specific enolase), and renal function (estimated glomerular filtration rate). The MAP72 group had a significantly higher mean arterial pressure, with a mean difference of 5 mm Hg (p=0.03). However, there were no significant differences in biomarkers of organ injury between the two groups after 48 hours. Renal replacement therapy was needed in 31% of the MAP65 group and 13% of the MAP72 group (p=0.14). The study concluded that double-blind allocation to different mean arterial pressure targets is feasible in comatose out-of-hospital cardiac arrest patients, but a mean arterial pressure target of 72 mm Hg did not result in improved biomarkers of organ injury compared to 65 mm Hg, although there was a numerically larger number of patients with preserved renal function in the MAP72 group.[10]

Recently, a randomised double-blind trial aimed to assess the effect of different blood pressure levels on global cerebral metabolism in comatose patients resuscitated from out-of-hospital cardiac arrest. In a double-blinded trial, 60 comatose patients were randomly assigned to low (63 mm Hg) or high (77 mm Hg) mean arterial blood pressure. The primary outcome was time-averaged means of cerebral energy metabolites between groups. Despite clear separation in mean arterial pressures between the groups (15 mm Hg; P<0.001), cerebral biochemical variables were not significantly different (lactate-pyruvate ratio, low MAP 19 (16–31) vs. high MAP 23 (16–33), P=0.64). The lactate-pyruvate ratio remained high (> 16) in both groups during the first 30 hours. Cerebral lactate > 2.5 mM, pyruvate levels > 110 µM, lactate-pyruvate ratio > 30, and glycerol > 260 µM during the first 24 hours were highly predictive for poor neurological outcome and death with an area-under-the-curve of 0.80. The study concluded that targeting a higher mean arterial pressure within 180 min of the return of spontaneous circulation did not significantly improve cerebral energy metabolism within 96 hours of post-resuscitation care. Poor clinical outcomes were associated with worse biochemical patterns.[25]

Should we routinely target a higher or lower blood pressure target in comatose patients post cardiac arrest?

No, not based on the results of the BOX trial. However, further work is required to determine if a personalised approach can be used based on phenotyping.

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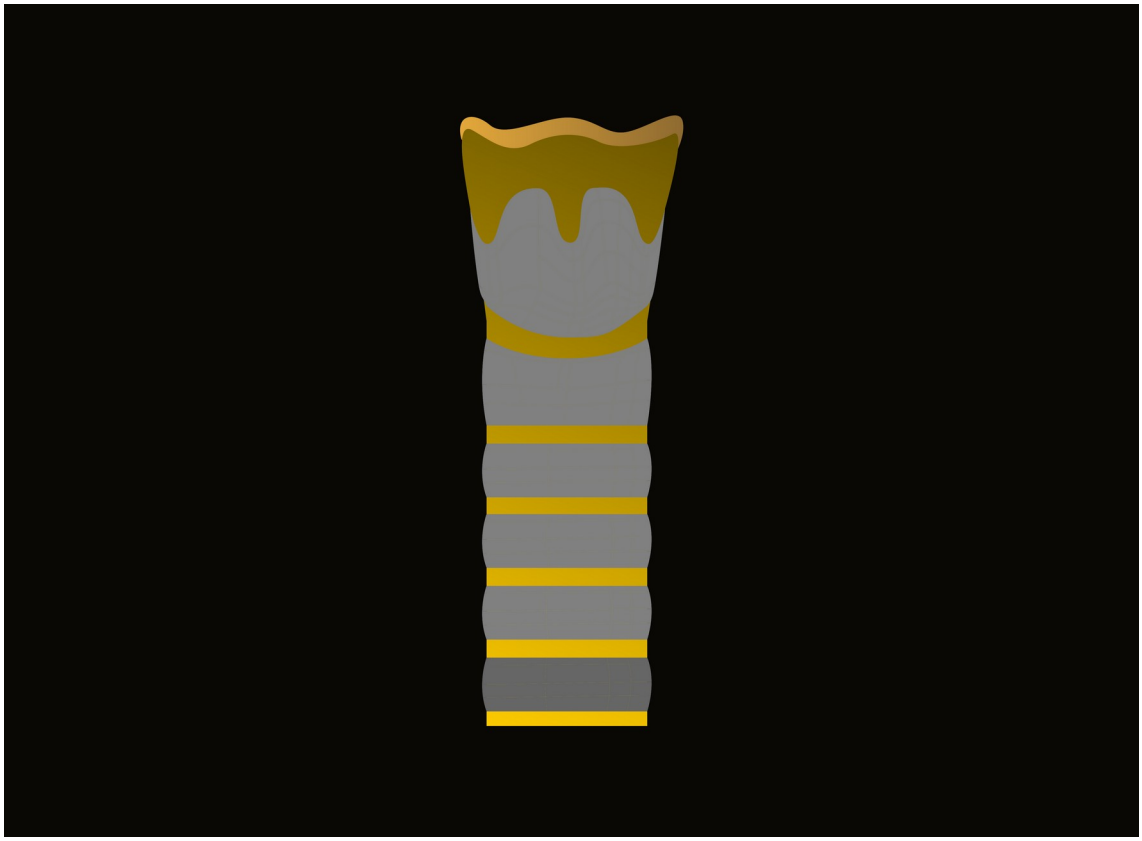

Airway Trials

PREPARE II

Russell DW, Casey JD, Gibbs KW, Ghamande S, Dargin JM, Vonderhaar DJ, et al. Effect of Fluid Bolus Administration on Cardiovascular Collapse Among Critically Ill Patients Undergoing Tracheal Intubation: A Randomized Clinical Trial. JAMA 2022;328(3):270–9

Introduction

Emergency endotracheal intubation (ETI) is a common life-saving procedure performed in the United States and around the world. Approximately 15 million ETIs are performed annually in the operating room in the U.S.A, and an additional 650,000 hospital intubations occur outside the operating room, including 346,000 in the emergency department (ED).[1]

The global INTUBE study[2] recorded a 46% incidence of cardiovascular instability during episodes of emergency intubation in the critically ill. Across the 2964 patients from 197 countries in 5 continents, 3.1% receiving emergency intubation suffered a cardiac arrest. Older data has reported a 30-fold increase in peri-intubation adverse events in the emergency department compared with intubations in the operating theatre.[3]

The pathophysiology of post-intubation hypotension and circulatory collapse is multifactorial, including decreased venous return secondary to positive pressure ventilation, reduced cardiac output from the negatively inotropic anaesthetic agents used, as well as the acute illness and underlying patient factors, such as chronic heart failure. The impediment of venous return, which determines cardiac preload and thus cardiac output, is particularly relevant in patients whose circulation was barely adequate prior to positive pressure ventilation.

Fluid bolus therapy is recommended by several national and international guidelines,[4–6] despite a paucity of evidence to support this practice. The preceding PREPARE trial[7] investigated whether a fluid bolus at the time of emergency intubation would prevent or diminish circulatory instability. While a 500 ml fluid bolus had little effect on the incidence of circulatory collapse, the subgroup of patients receiving positive pressure ventilation may have benefited.

Synopsis

PREPARE II was a multi-centre, parallel-group, unblinded, pragmatic randomised clinical trial conducted across 11 intensive care units (ICUs) in the US, aiming to compare the administration of an intravenous fluid bolus versus no fluid bolus for critically ill adults undergoing tracheal intubation.

Eligible patients were critically ill adults planned for tracheal intubation with specific anaesthesia and positive pressure ventilation strategies. Patients were excluded based on criteria such as pregnancy, incarceration, immediate intubation need that negated randomisation, or clinician-determined fluid bolus necessity or contraindication.

The randomization process involved a 1:1 ratio, and was stratified according to trial sites using randomly permuted block sizes of 2, 4, and 6. The study participants were either administered an intravenous fluid bolus or were not, depending on the group they were assigned to. The fluid bolus group received a 500 mL isotonic crystalloid solution, infused intravenously before and during the intubation procedure, while the other group did not receive a fluid bolus except under specific conditions like hypotension.

The primary outcome was focused on cardiovascular collapse, defined by multiple indicators such as new or increased vasopressor use, systolic blood pressure drop, cardiac arrest, or death. The secondary outcome pertained to the incidence of death prior to the 28th day. Data was collected throughout the procedure and post-procedure from electronic health records.

Sample size was determined assuming a 25% rate of cardiovascular collapse in the no fluid bolus group and anticipating less than 5% missing data for the primary outcome. This led to a calculated sample size of 750 patients for an 80% power at a 2-sided α level of .05 to detect an absolute difference of 8.75% between groups. However, due to a lower observed incidence of cardiovascular collapse than expected, the sample size was increased to 1065 patients.

The primary statistical analysis was an unadjusted comparison of the primary outcome between the two groups using the x2 test. This analysis was supported by sensitivity analyses using alternative definitions and analysis methods. Additional analyses, including a generalized linear mixed-effects model and a logistic regression model, were also performed. Furthermore, an interim analysis was conducted after the enrolment of 375 patients. The secondary and exploratory outcomes were compared using the x2 test for categorical outcomes and the Mann-Whitney test for continuous variables. The data analysis was performed using R version 4.1.0.

A total of 1576 patients were initially screened for this clinical trial concerning tracheal intubation. After excluding 509 individuals due to various reasons such as the urgency of the procedure, contraindication or need for a fluid bolus, and others, 1067 participants were recruited and randomised for the study. However, two individuals were subsequently removed due to incarceration, leaving 1065 patients for the primary analysis.

These patients were divided into two groups: 538 were allocated to the fluid bolus (FB) group and 527 to the no fluid bolus (no FB) group. The median age was 62 years with a roughly equal distribution of males and females (approximately 42.1% women). The predominant indication for tracheal intubation was acute respiratory failure, affecting about 60% of patients. Additionally, around 20% of the patients were on vasopressors, and 10% were receiving intravenous fluids at the time of enrolment, indicating a moderately severe illness burden.

Nearly all patients (99.4%) in the FB group received an intravenous fluid bolus of a median volume of 500 millilitres (mL) between enrolment and induction of anaesthesia. Conversely, in the no FB group, a minimal proportion (1.1%) received an intravenous fluid bolus, with a median volume of 0 mL. The approach to pre-oxygenation, choice of anaesthetic agents, systolic blood pressure, and oxygen saturation levels at induction did not significantly differ between the two groups, suggesting no significant confounding factors.

Regarding the primary outcome, cardiovascular collapse occurred in 21.0% of the FB group and 18.2% of the no FB group. However, this difference was not statistically significant, with an absolute difference of 2.8% (95% Confidence Interval, -2.2% to 7.7%; P=0.25). Thus, the administration of a fluid bolus did not significantly reduce the incidence of cardiovascular collapse in any prespecified subgroup.

For secondary outcomes, the 28-day mortality rate was slightly lower in the FB group (40.5%) compared to the no FB group (42.3%). However, this difference did not reach statistical significance (absolute difference, -1.8%; 95% CI, -7.9% to 4.3%; P=0.55).

Finally, in terms of harms, no significant differences were observed between the two groups regarding the components of the cardiovascular collapse composite outcome, including new or increased vasopressor usage, systolic blood pressure below 65 mm Hg, cardiac arrest, and death.

In conclusion, the study demonstrates that administering a fluid bolus prior to tracheal intubation did not significantly alter the risk of cardiovascular collapse, mortality rate, or other health measures in this patient population.

Critique

PREPARE II was a superbly designed and executed airway trial which sought to answer a common and important question – would this critically ill patient benefit from an intravenous fluid bolus at the time of emergency intubation. It was robust for several reasons. Firstly, it was a multi-centre, parallel-group, unblinded, pragmatic randomized clinical trial, which enhances the generalisability of the findings and reduces the likelihood of bias from single-centre studies. It was conducted at 11 intensive care units across the United States with a diverse patient population of critically ill adults undergoing tracheal intubation. The trial employed a 1:1 randomization ratio with stratification according to trial site, which ensures balance in patient characteristics across intervention groups. The intervention itself was clearly defined and distinct, with one group receiving a 500-mL intravenous fluid bolus and the other group not receiving a fluid bolus except as treatment for hypotension or if the operator determined that an intravenous fluid bolus was necessary for the safety of the patient. Data collection was meticulous, with personnel trained according to the trial protocol collecting data during the procedure, including the volume of intravenous fluid administered, the lowest levels of systolic blood pressure and oxygen saturation, and initiation of or increased dose of vasopressors. The trial's robustness is further supported by the high completion rate, with 99.8% of the randomized patients completing the trial and being included in the primary analysis.

Despite the robustness of the trial design, the PREPARE II trial did have some potential limitations and sources of bias. First, the trial was unblinded, which can introduce performance bias as the knowledge of the treatment assignment may influence the conduct of the procedure. This may be magnified if the operator is allocated to practice at odds with his or her usual practice. However, from the available data, there is little to suggest practice differed between the two groups, with similar rates of vasopressor administration between groups (~12%) and similar rates of positive pressure ventilation between induction of anaesthesia and laryngoscopy (97%).

Furthermore, although the trial was conducted at multiple sites to enhance generalisability, all sites were located within the United States, which may limit the generalisability of the findings to other countries with different healthcare systems, practices, or patient populations.

Another possible limitation is that the fluid bolus administration was left to the operator's discretion, which could introduce variability in the timing and speed of the fluid administration, potentially influencing the outcomes. While the trial used predictive enrichment to recruit a specific population thought more likely to benefit (those receiving positive pressure), it also introduced a selection bias, skewing the patient population towards those with certain clinical characteristics, limiting the generalisability of the results to all critically ill adults undergoing tracheal intubation, including the sickest requiring immediate intubation.

An over-riding strength of PREPARE-II is the coherence of its results across the varying outcomes and subgroups. There was no signal of benefit, which is useful clinical information. Perhaps clinicians should focus on something else when intubating the sickest patients in the hospital.

Body of Evidence

Only one other randomised controlled trial has examined the question of intravenous fluid administration at the time of intubation in the critically ill. The PREPARE trial[7] preceded PREPARE II and informed its design. PREPARE was a pragmatic, multi-centre, unblinded, randomised trial conducted across nine sites in the USA, including eight ICUs and one emergency department. The trial involved critically ill adults aged 18 years and above who were undergoing tracheal intubation. Participants were randomly assigned to either receive an intravenous infusion of 500 mL of crystalloid solution or no fluid bolus. The primary outcome was cardiovascular collapse, defined as a new systolic blood pressure of less than 65 mm Hg; new or increased use of vasopressors between induction and 2 minutes after tracheal intubation; or cardiac arrest or death within 1 hour of tracheal intubation. PREPARE was conducted from February, 2017, to January, 2018, and was terminated early due to futility, after 337 adults had been randomly assigned.

The primary outcome, cardiovascular collapse, was observed in 20% of patients in the fluid bolus group and 18% of patients in the no fluid bolus group, representing an absolute difference of 1.3%, which was not statistically significant. The individual components of the cardiovascular collapse composite outcome did not differ significantly between the two groups either. In-hospital mortality was also not significantly different between the fluid bolus group (29%) and the no fluid bolus group (35%). Interestingly, in subgroup analysis, patients receiving positive pressure ventilation had a reduced incidence of cardiovascular collapse with a fluid bolus, while those not receiving positive pressure ventilation had a higher incidence of circulatory collapse than those not receiving fluid.

Should we routinely administer fluid therapy to critically ill patients undergoing endotracheal intubation?

No, the PREPARE and PREPARE II trials do not support this practice.

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Respiratory Trials

PILOT

Semler MW, Casey JD, Lloyd BD, Hastings PG, Hays MA, et al. Oxygen-Saturation Targets for Critically Ill Adults Receiving Mechanical Ventilation. N Engl J Med 2022;387:1759-69

Introduction

In the United States, over 2 million people receive invasive mechanical ventilation annually, including an estimated 20–40% of all individuals admitted to intensive care units (ICUs).[1,2] Up to one-third of critically ill patients requiring mechanical ventilation do not survive.[3] Once on a ventilator, the level of supplemental oxygen needs to be prescribed, with much uncertainty over the optimal oxygenation level to be targetted. Both hypoxia and hyperoxia are abnormal states and are are unlikely to be beneficial, although where the threshold for harm occurs is unclear, and also likely to be patient specific.

Severe hypoxaemia can induce irreversible neuronal damage in as little as 3 minutes.[4] The effect of longer periods of milder hypoxia in critically ill patients is less clear. Hyperoxia has also be associated with harm across a range of conditions, including myocardial infarction,[5] cardiac arrest,[6] stroke[7] and sepsis.[8]

Over the past decade, a number of large, multi-centre, randomised controlled trials have compared low-normal with high-normal with conflicting results. Observational data suggests a U shaped curve, where an intermediate level of oxygenation, avoiding the risks of hypoxia and hyperoxia, may be best.[9] However, to date, no randomised controlled trial has incorporated low-normal, intermediate and high-normal oxygenation targets.

Synopsis

PILOT (Pragmatic Investigation of Optimal Oxygen Targets) was a pragmatic, unblinded, cluster-randomised, cluster-crossover trial undertaken at the medical ICU and emergency department of Vanderbilt University Medical Center in Nashville, USA. It compared three distinct oxygen saturation (SpO_2) targets during invasive mechanical ventilation in critically ill adults.

Inclusion criteria were adults aged 18 years and above who required invasive mechanical ventilation. Exclusion criteria included pregnancy and incarceration. Patients were enroled at the commencement of invasive mechanical ventilation.
The chosen SpO_2 targets were lower (90%), intermediate (94%), and higher (98%). During the trial, respiratory therapists adjusted the fraction of inspired oxygen (FiO_2) to achieve the target SpO_2. The goal was to begin this adjustment within 15 minutes after the initiation of mechanical ventilation and to continue until the discontinuation of mechanical ventilation, transfer out of a participating unit, or the end of the 2-month study period. Other aspects of mechanical ventilation were determined by the treating clinical team.

The process of allocation involved assigning all eligible patients in the emergency department and ICU as a single cluster to an SpO_2 target. The departments switched between the three SpO_2 targets every two months, following a randomly generated sequence, for 36 months. This sequence was computerized and used permuted blocks of three to minimize the effect of seasonal variation and temporal changes. To ensure that data from new patients did not interfere with the analysis, the final seven days of each two-month period were considered an analytic washout period.

The primary outcome was the number of days alive and free of mechanical ventilation through day 28. This was calculated as the number of calendar days alive and free of invasive mechanical ventilation beginning the day after the final receipt of invasive mechanical ventilation through day 28. The only secondary outcome was death from any cause by day 28.

The sample size of 2250 patients was determined using data from a previous trial conducted in a similar clinical context. This sample size would provide a power of 92% at a two-sided alpha level of 0.05 to detect an absolute difference of 2 ventilator-free days between any two of the three trial groups.

The primary analysis used a proportional-odds model to compare the number of ventilator-free days among patients assigned to the lower-, intermediate-, and higher-target groups. Additional sensitivity analyses using alternative definitions of the trial population and alternative statistical methods were planned. The data and safety monitoring board undertook an interim analysis of patients enroled during the first 18 months of the trial.

Enrolment began in July 2018, paused during the peak of the Covid-19 pandemic, and concluded in August 2021. Out of the initial 3024 patients screened, 2987 were enrolled

in the study, with 2541 included in the primary analysis after excluding ineligible participants.

The study collected a substantial amount of oxygen saturation (SpO_2) and fractional inspired oxygen (FiO_2) data. For the SpO_2 values, the medians for the lower, intermediate, and higher-target groups were 94%, 95%, and 97%, respectively. The percentage of all SpO_2 measurements with a value of 99% or 100% was 12.3% in the lower-target group, 14.7% in the intermediate-target group, and 32.7% in the higher-target group. The percentage of measurements with a value less than 85% was 0.8%, 0.6%, and 0.9%, respectively. Hypoxaemia incidence and duration, characterized by SpO_2 values less than 85%, 80%, or 70%, were similar across all groups.

Regarding the FiO_2 values, the medians for the lower, intermediate, and higher-target groups were 0.31, 0.37, and 0.45, respectively. The percentages of FiO_2 values equivalent to ambient air (0.21) were 33.8%, 21.9%, and 4.0%, respectively. FiO_2 values that were 0.40 or higher were found in 32.6%, 44.9%, and 69.1% of measurements, respectively.

In terms of primary outcome, the number of ventilator-free days up to the 28th day did not differ significantly among the trial groups. The median was 20 days for the lower-target group, 21 days for the intermediate-target group, and 21 days for the higher-target group. There was no significant difference in this outcome across the groups (P=0.81).

By day 28, the mortality rates before hospital discharge were 34.8% for the lower-target group, 34.0% for the intermediate-target group, and 33.2% for the higher-target group. No significant difference in mortality was detected among the groups. The incidence of certain safety outcomes, including cardiac arrest, arrhythmia, myocardial infarction, ischaemic stroke, and pneumothorax or pneumomediastinum, was also similar among the groups.

Critique

The Pragmatic Investigation of Optimal Oxygen Targets (PILOT) trial was a cluster-randomized, cluster-crossover trial conducted at a single centre, focusing on adult patients receiving mechanical ventilation. The study compared three groups with differing oxygenation targets: low (88-92%), intermediate (92-96%), and high (96-100%). The primary outcomes measured were the number of ventilator-free days through day 28, and the secondary outcome was death by day 28. The trial included 2,541 patients and found no significant difference in ventilator-free days or 28-day mortality between the groups.

Strengths of the PILOT trial include its large sample size, minimal exclusion (just 1% of screened patients) and the immediate enrolment of patients upon receipt of mechanical ventilation. This approach provided robust data and minimized potential delays that might confound the outcomes. The baseline characteristics and interventions (such as positive end-expiratory pressure, choice of sedation, and ventilator weaning) were similar between the groups, further strengthening the comparability of the results. Additionally, the trial's design ensured fidelity of intervention and the collection of granular data related to oxygen targets, FiO_2, and the incidence of hypoxaemia, enhancing its internal validity.

However, the PILOT trial also has some limitations. As a single-centre trial, its results may not be generalisable to other patient populations or healthcare settings. The patient population was restricted to medical patients, meaning the findings might not apply to surgical or trauma patients. The open-label nature of the trial can unconsciously bias treating clinicians decision making. Furthermore, the study neither confirmed nor refuted treatment effects of a plausible magnitude, which means that smaller, yet clinically significant differences between the groups might have been overlooked. Lastly, the trial was unable to confirm or refute a heterogeneity of treatment effect, which suggests that the impact of different oxygen targets might vary among patient subgroups.

The lack of a significant difference between the three groups could be due to several factors. It is possible that the effects of different oxygen targets are subtle and may not manifest as changes in outcomes such as ventilator-free days or 28-day mortality, especially in a heterogeneous population of critically ill patients, such as more subtle cognitive defects. There may also be confounding factors that were not fully accounted for in the study design.

The low oxygenation group had a target SpO2 of 90% (88% - 92%) but achieved a median value of 94%. This exemplifies the difficulties in maintaining target groups, as for those with healthier lungs, it proved difficult to achieve the low target saturations.

Regardless of these small issues, PILOT is the largest oxygenation target trial to date and further supports the concept that across a relatively normal target oxygenation ranges, outcomes are similar. The next major advancement in this field will be the completion of the 40,000 patient MEGA-ROX trial. Until then, small, but clinically relevant treatment effects, will remain obscured from conventional sample sizes.

Body of Evidence

O2-ICU was a multi-centre randomised clinical trial conducted in four ICUs in the Netherlands. It assessed whether a low-normal PaO_2 target could reduce organ dysfunction in critically ill patients with systemic inflammatory response syndrome (SIRS) as compared to a high-normal target. The trial was carried out from February 2015 to January 2019. Of the 9925 patients screened, 574 patients who met two or more SIRS criteria and were expected to stay in ICU for more than 48 hours were included. The participants were allocated into two groups, with 205 in the low-normal target PaO_2 range (8 to 12 kPa) and 195 in the high-normal range (14 to 18 kPa). An inspired oxygen fraction greater than 0.60 was only applied when clinically necessary. The primary outcome was the $SOFA_{RANK}$ score, which is a ranked outcome of non-respiratory organ failure as quantified by the non-respiratory components of the Sequential Organ Failure Assessment (SOFA) score over the first 14 days of the study. The participants were ranked from those with the fastest organ failure improvement (lowest scores) to those with worsening organ failure or death (highest scores). Among the 574 patients randomized, 400 (70%) were enrolled within 24 hours, all of whom completed the trial. The median PaO_2 difference between the groups was -1.93 kPa (95% CI, -2.12 to -1.74; P<0.001). The $SOFA_{RANK}$ score was not significantly different between the low-normal PaO_2 group (-35 points) and the high-normal PaO_2 group (-40 points), with a median difference of 10 (95% CI, 0 to 21; P=0.06). There was no significant difference in the duration of mechanical ventilation (median difference, -0.15; 95% CI, -0.88 to 0.47; P=0.59) and in-hospital mortality (odds ratio, 1.04; 95% CI, 0.67 to 1.63; P=0.91) between the two groups. However, mild hypoxaemic measurements were more frequent in the low-normal group (1.9% vs 1.2%; median difference, 0.73; 95% CI, 0.30 to 1.20; P < 0.001). Rates of acute kidney failure and acute myocardial infarction rates were similar in both groups.

The multi-centre HOT-ICU[10] trial recruited 2928 adult patients, who were recently admitted to the ICU (≤12 hours before randomisation) and receiving significant oxygen therapy (either at least 10 L/min in an open system or a FiO_2 of at least 0.50 in a closed system). They were randomised to two different oxygen therapy targets, of either a PaO_2 of 60 mm Hg (lower-oxygenation group) or 90 mm Hg (higher-oxygenation group). The primary outcome, 90-day mortality, was similar in both groups, being 42.9% in the lower-oxygenation group and 42.4% in the higher target group (aRR, 1.02; 95% CI, 0.94 to 1.11; P=0.64). Other outcomes were also similar, including the percentage of days that patients were alive without life support, and the percentage of patients experiencing new episodes of shock, myocardial ischaemia, ischaemic stroke, or intestinal ischaemia.

In the multi-centre randomised LOCO2 trial,[11] patients suffering from acute respiratory distress syndrome (ARDS) were allocated to two distinct oxygen therapy regimens for a

period of 7 days. The conservative oxygen therapy group aimed for a target PaO_2 of 55 to 70 mm Hg, and an oxygen saturation (SpO_2) of 88 to 92%. Conversely, the liberal oxygen therapy group aimed for a higher target PaO_2 of 90 to 105 mm Hg, and an SpO_2 of ≥96%. The same mechanical ventilation strategies were implemented in both groups. The primary outcome under evaluation was mortality from any cause at 28 days. The trial was halted prematurely after the enrolment of 205 patients due to safety concerns raised by the data and safety monitoring board and the low likelihood of a significant difference between the two groups in the primary outcome. By day 28, 34 of 99 patients (34.3%) in the conservative-oxygen group had died and 27 of 102 patients (26.5%) in the liberal-oxygen group (difference, 7.8%; 95% CI, -4.8 to 20.6). By day 90, mortality was 44.4% in the conservative-oxygen group and 30.4% in the liberal-oxygen group (difference, 14.0%; 95% CI, 0.7 to 27.2). Five instances of mesenteric ischaemia were reported in the conservative-oxygen group.

The ICU-ROX[12] randomised trial included 1000 adult patients in the ICU who were expected to need mechanical ventilation beyond the day after recruitment. The patients were assigned to receive either conservative or usual oxygen therapy. For both groups, the minimum acceptable oxygen saturation, as measured by pulse oximetry (SpO_2), was set at 90%. In the conservative-oxygen group, an alarm was set to sound when SpO_2 reached 97% and the fraction of inspired oxygen (FiO_2) was reduced to 0.21 if SpO_2 was above the minimum acceptable limit. The usual-oxygen group received standard care, with no specific limits on FiO_2 or SpO_2. The primary outcome was the number of ventilator-free days from the time of randomization until day 28. The results showed no significant difference between the two groups in terms of ventilator-free days. The conservative-oxygen group had a median of 21.3 days (interquartile range, 0 to 26.3) and the usual-oxygen group had a median of 22.1 days (interquartile range, 0 to 26.2), yielding an absolute difference of -0.3 days (95% CI, -2.1 to 1.6; P=0.80). However, the conservative-oxygen group spent more time in the ICU with an FiO_2 of 0.21 (median of 29 hours) than the usual-oxygen group (median of 1 hour), and less time with an SpO_2 exceeding 96%. At 180 days, mortality rates were similar in both groups, with 35.7% in the conservative-oxygen group and 34.5% in the usual-oxygen group, resulting in an unadjusted odds ratio of 1.05 (95% CI, 0.81 to 1.37).

The Oxygen-ICU trial[13] was a single-center, open-label, randomised trial conducted from March 2010 to October 2012 at Modena University Hospital in Italy. The study aimed to determine whether a conservative oxygenation protocol could improve outcomes in adult patients expected to stay in the ICU for at least 72 hours. Although the original plan was to recruit 660 patients, the trial was concluded early after enrolling 480 participants due to enrolment difficulties. In the conservative group, oxygen therapy was administered to maintain PaO_2 levels between 70 and 100 mm Hg or arterial

oxyhaemoglobin saturation (SpO_2) between 94% and 98%. In contrast, the conventional group received standard ICU practice, allowing PaO_2 values up to 150 mm Hg or SpO_2 values between 97% and 100%. The primary outcome was ICU mortality, while secondary outcomes included the incidence of new organ failure and infections 48 hours or more after ICU admission. Among the 434 patients (median age, 64 years; 43.3% women) included in the modified intent-to-treat analysis, the conservative group had significantly lower daily time-weighted PaO_2 averages during the ICU stay (median PaO_2, 87 mm Hg) compared to the conventional group (median PaO_2, 102 mm Hg) (P<0 .001). Importantly, ICU mortality was lower in the conservative group (11.6%) than in the conventional group (20.2%), resulting in an absolute risk reduction (ARR) of 0.086; 95% CI, 0.017 to 0.150; RR, 0.57; 95% CI, 0.37 to 0.90; P=0.01). Furthermore, the conservative group had lower incidences of new shock episodes, liver failure, and bloodstream infections.

Panwar and colleagues[14] investigated the feasibility of a conservative oxygenation strategy as an alternative to a liberal oxygenation strategy among ICU patients who were anticipated to require invasive mechanical ventilation (IMV) for at least 24 hours. The trial was conducted across four multidisciplinary ICUs and included 103 adult patients. Patients were randomly allocated to two groups: a conservative oxygenation strategy group, with a target oxygen saturation as measured by pulse oximetry (SpO2) of 88–92% (n = 52) and a liberal oxygenation strategy group with a target SpO2 of ≥96% (n = 51). The groups separated well, with differences in SpO_2, SaO_2, PaO_2, and FiO_2 between the two groups. The time spent with SpO_2 less than 88% was slightly higher in the conservative arm (1% vs. 0.3%, P=0.03), while the time spent with SpO_2 greater than 98% was significantly lower in the conservative arm (4% vs. 22%, P<0.001). For the primary outcome of 90-day mortality, the adjusted hazard ratio for the conservative arm was 0.77 (95% CI, 0.40 to 1.50; P=0.44) overall and 0.49 (95% CI, 0.20 to 1.17; P=0.10) in a prespecified subgroup of patients with a baseline PaO_2/FiO_2 less than 300. There were no significant between-group differences in new organ dysfunction measures, or in ICU or 90-day mortality.

BOX-Oxygen – The oxygenation arm of the BOX trial[15] sought to assess whether a restrictive or liberal oxygen target had different impacts on comatose adults who experienced out-of-hospital cardiac arrest. In this 2-by-2 factorial randomized trial, patients were randomised in a 1:1 fashion into two groups, with 394 in the restrictive oxygen target group (PaO2 of 9 to 10 kPa or 68 to 75 mm Hg) and 395 in the liberal oxygen target group (PaO2 of 13 to 14 kPa or 98 to 105 mm Hg). The primary outcome was a composite of death from any cause or hospital discharge with severe disability or coma (as measured by a Cerebral Performance Category (CPC) of 3 or 4) within 90 days. The trial also considered secondary outcomes such as neuron-specific enolase levels at

48 hours, death, cognitive ability as scored by the Montreal Cognitive Assessment, disability level as scored by the modified Rankin scale, and CPC at 90 days. The primary outcome occurred in 32.0% of the restrictive-target group and 33.9% of the liberal-target group (hazard ratio, 0.95; 95% CI, 0.75 to 1.21; P=0.69). By 90 days, 28.7% of patients in the restrictive-target group and 31.1% in the liberal-target group had died. Median scores for CPC, the modified Rankin scale, and the Montreal Cognitive Assessment were similar in both groups. At 48 hours, the median neuron-specific enolase level was slightly lower in the restrictive-target group. No significant difference in the incidence of adverse events was observed between the two groups.

The EXACT[16] randomised clinical trial aimed to investigate the impact of targeting a lower oxygen saturation in the early stages of post-resuscitation care for out-of-hospital cardiac arrest on survival to hospital discharge. The study was conducted across 2 emergency medical services and 15 hospitals in Victoria and South Australia from December 2017 to August 2020, and involved unconscious adults with return of spontaneous circulation and a peripheral oxygen saturation (Spo2) of at least 95% while on 100% oxygen. The trial included 428 out of a planned 1416 patients, with the study ending early due to the COVID-19 pandemic. Patients were randomised by paramedics to receive oxygen titration to either 90% to 94% (intervention group, n=216) or 98% to 100% (standard care group, n=212) until their arrival in the ICU. The primary outcome was survival to hospital discharge. Nine secondary outcomes, including hypoxic episodes (SpO2 <90%) and prespecified serious adverse events such as hypoxia with rearrest, were also collected. The primary analysis included 425 patients (median age, 65.5 years; 23.5% women). Survival to hospital discharge occurred in 38.3% of the intervention group and 47.9% of the standard care group (difference, -9.6%; 95% CI, -18.9% to -0.2%; unadjusted odds ratio, 0.68; 95% CI, 0.46 to 1.00; P=0.05), indicating lower survival in the intervention group. Among the 9 secondary outcomes, 8 showed no significant difference between the groups. However, hypoxic episodes prior to ICU were significantly higher in the intervention group (31.3%) compared to the standard care group (16.1%) (difference, 15.2%; 95% CI, 7.2% to 23.1%; OR, 2.37; 95% CI, 1.49 to 3.79; P< 0001).

Cumpstey and colleagues[17] completed a recent systematic review and meta-analysis incorporated data from eight clinical trials, involving a total of 4,415 participants. All trials were considered to have a high risk of bias with no single study considered low risk in all assessed domains. There was no significant difference in mortality rates when comparing higher and lower oxygen targets, with an odds ratio of 0.95 (95% CI, 0.74 to 1.22). However, the clinical significance of this finding is compromised due to considerable variation and overlap in the oxygen target ranges across different studies.

When comparing normoxaemia with hyperoxaemia, data from seven studies involving 4,245 participants suggested a potential reduction in mortality at the longest follow-up for those targeted for normoxaemia, with an odds ratio of 0.73 (95% CI, 0.57 to 0.95). Despite this finding, the certainty of this estimate was deemed very low, suggesting the need for further investigation. Finally, when comparing relative hypoxaemia with normoxaemia, there was no significant difference in mortality rates (OR, 1.20; 95% CI, 0.83 to 1.73). Further research is required to confirm these findings due to the low certainty of the available data.

In critically ill, mechanically ventilated patients should we routinely target a specific SpO_2

Based on the data from the PILOT trial, outcomes appear similar across a broad range of target oxygen levels in the critically ill. Individual factors will need to be considered however.

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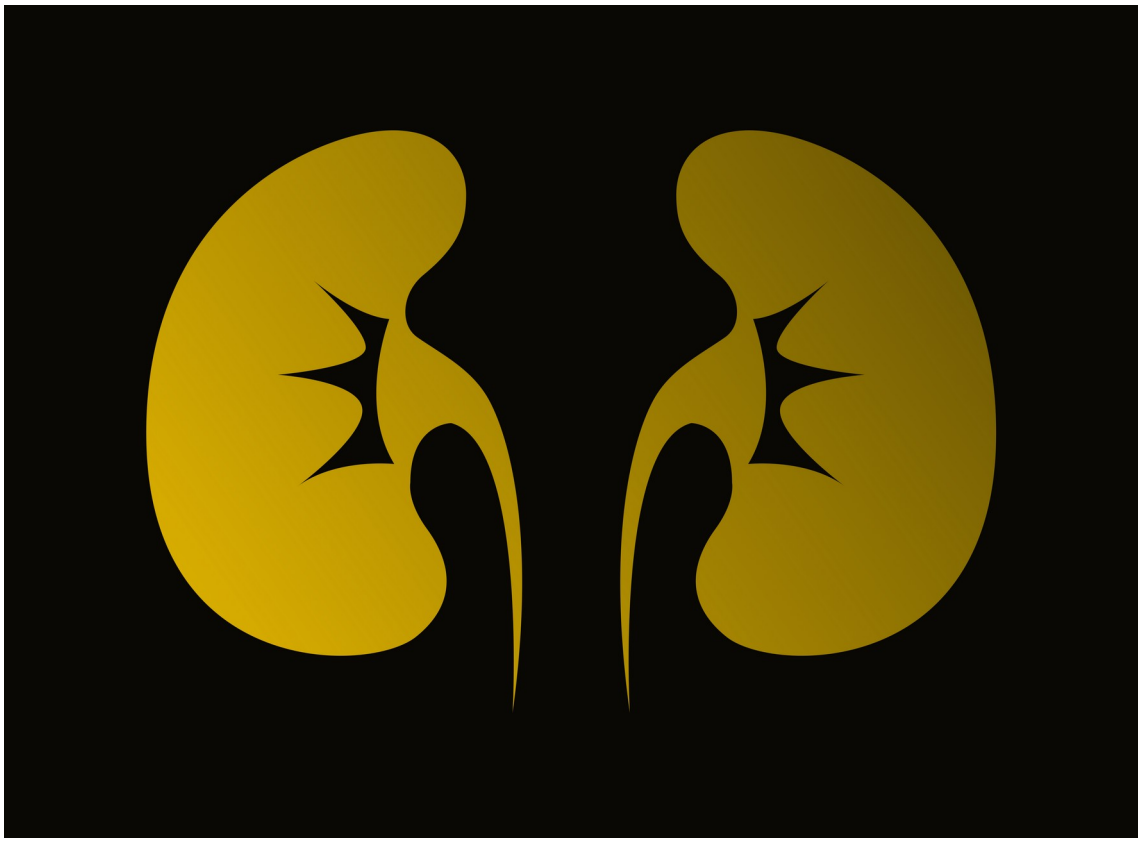

Renal Trials

Contrast RISK

Kjaergaard J, Møller JE, Schmidt H, Grand J, Mølstrøm S, Borregaard B, et al. Blood-Pressure Targets in Comatose Survivors of Cardiac Arrest. N Engl J Med. 2022 Oct 20;387(16):1456-1466

Introduction

Contrast-associated acute kidney injury (CA-AKI) has been defined as the onset of acute renal impairment following the administration of iodinated contrast media [1]. Nephrotoxicity may occur via vasoconstriction, oxidative stress, osmotic tubular nephrosis, and ischaemia of the outer medulla.[1,2] The kidneys are particularly susceptible to the injurious effects of contrast media due to a combination of variable regional renal perfusion and high metabolic demand.[2] Exposure to contrast media during contrast angiography and percutaneous coronary intervention (PCI) are leading causes of CA-AKI.[3]

The onset of CA-AKI is further complicated through association with increased morbidity and mortality. In addition to requiring emergent dialysis and increasing length of hospital stay, it has been demonstrated that patients with CA-AKI are at increased risk of developing cardiogenic shock, pulmonary oedema, cardiac conduction defects and chronic kidney disease.[4,5]

Furthermore, CA-AKI has significant economic implications and incurs an annual cost of over $400 million in the United States.[6] A large French retrospective cross-sectional population-based study by Aubry and colleagues investigated cases of CA-AKI following image guided cardiac procedures in 1,047,329 hospitalisations.[7] The study revealed a frequency of CA-AKI of 3.1% and established that mean length of stay (20.5 vs 4.7 days, P<0.00001) and cost of hospitalisation (€15,765 vs €3,352, P<0.0001) were higher in those with CA-AKI.

Therefore, the ability to reduce the incidence of CA-AKI has important implications.

Synopsis

James et al. conducted a pragmatic, stepped-wedge, cluster randomised control trial which investigated a multifaceted intervention aimed at reducing the incidence of CA-AKI. The study intervention consisted of physician education, clinical decision support

and audit with feedback.[7] The intervention was delivered to invasive cardiologists at 3 cardiac catheterisation laboratories in Alberta, Canada. Contrast RISK was published in the Journal of the American Medical Association on 6th September 2022. Contrast RISK tested the hypothesis that a clinical decision support system combined with education, audit and feedback would reduce the incidence of CA-AKI following intra-arterial contrast administration during cardiac catheterisation. Contrast RISK trial is a pragmatic, stepped-wedge, cluster randomised clinical trial. The trial included 34 invasive cardiologists working at 3 catheterisation laboratories in 1 region of Canada. All 34 invasive cardiologists contributed to the control (pre-intervention) period of the trial. However, three physicians retired prior to receiving the intervention.

Between 1st January 2018 and 1st September 2019, the cardiologists were randomly assigned 1 of 8 start dates for the intervention. Randomisation occurred using computer-generated random numbers and was stratified by clusters with 3-6 physicians per cluster depending on each physician's site and practice group. The stepped wedge approach of this trial ensured that by the end of the study all practising physicians had been exposed to the intervention.

Due to the nature of the intervention, blinding of the physicians, catheterisation unit staff, and members of the research team was not possible. Eligible patients included those aged 18 years or older at the time of the procedure with a greater than 5% risk of AKI based on the National Cardiovascular Data Registry multi-variable AKI risk prediction model.

Patients were excluded if they were undergoing dialysis or receiving emergency primary PCI for an ST-segment elevation myocardial infarction (STEMI). Dialysis patients were excluded based on an inability to detect changes in post-procedural serum creatinine levels. STEMI patients were excluded due to the time-sensitive nature of primary PCI. The trial intervention consisted of a bundle of interventions with an overall goal to reduce the incidence of CA-AKI following coronary angiography.

Firstly, physicians received an educational session which provided information on CA-AKI, prevention techniques and trial protocols. Secondly, they received clinical decision support which included automated individualised AKI risk prediction, graphic display of safe contrast volume targets, and calculation of haemodynamic-guided intravenous fluid volume targets tailored to left ventricular end-diastolic pressure measurements. The cardiologists received real-time guidance on safe patient-specific contrast volume targets coupled with alerts when the target was reached. Finally, regular audit and feedback provided physicians with information on contrast volume used relative to the safe contrast volume target, the administration of intravenous fluids compared with the

haemodynamic guided recommendations, and the incidence of AKI. The control group was the comparator in this trial and consisted of patients undergoing treatment by the invasive cardiologists prior to the intervention period. The physicians provided usual care and did not receive educational outreach, clinical decision support or audit and feedback. The primary outcome was the incidence of AKI as defined by an absolute increase in serum creatinine of ≥ 26 mmol/L (0.3 mg/dL) within 48 hours or a relative increase ≥ 50% within 4 days of the procedure, based on Kidney Disease: Improving Global Outcomes (KDIGO) guidelines.[8] The most recent available creatinine level prior to cardiac catheterisation was used as the baseline creatinine level with follow-up creatinine testing performed 48-96 hours post-procedure. Utilising historical data, James and colleagues anticipated a 10% incidence of CA-AKI in the study patient population. A prior prospective multicentre quality improvement study reported a 21% relative risk reduction in CA-AKI following the introduction of prevention initiatives.[9] Thus, it was calculated that 7270 procedures would provide 80% power to detect a 30% reduction in the primary outcome of AKI with an α level of 0.05.

Prespecified secondary clinical outcomes included the number of days in hospital within 30 days after a procedure, major adverse cardiovascular events (including death; hospitalisation for heart failure, angina, or myocardial infarction; or an unplanned revascularisation procedure), and major adverse kidney events (including death, acute dialysis, subsequent hospitalisation for AKI, or end-stage kidney disease within 1 year post-procedure).

Prespecified secondary process of care outcomes included the volume of contrast used, the proportion of procedures in which excessive contrast volume was used, the intravenous fluid volume administered for AKI prevention up to 6 hours post-procedure, and the proportion of procedures with insufficient fluid administration despite the haemodynamic-guided target. The effects on the primary outcome were examined in prespecified subgroup analyses according to age, sex, diabetes, heart failure, chronic kidney disease, procedure type, and baseline AKI risk.

As some cardiologists retired from practice prior to receiving the intervention, a post hoc analysis that excluded these physicians was performed.

29418 procedures were performed in 26110 patients during the study period. However, after exclusion of patients receiving dialysis therapy, undergoing PCI for a ST-elevation myocardial infarction and those with less than a 5% risk of AKI, there were 7820 procedures in 7106 patients eligible for inclusion. Of the 7820 procedures, 794 (10.2%) were missing data for the primary outcome and 698 (8.9%) were missing data on contrast volume.

The intervention group consisted of 31 invasive cardiologists who performed 4327 procedures on 4032 patients (mean age, 70.3 [SD, 10.7] years; 1384 were women [32.0%]) and the control group included 34 cardiologists who performed 3493 procedures among 3251 patients (mean age, 70.2 [SD, 10.8] years; 1151 were women [33.0%]). Baseline comorbidities, pre-procedure eGFR, predicted risk of AKI, and fluoroscopy time (a surrogate of procedure complexity) were similar between groups.

However, there were small differences in procedure indication between the study groups. Of particular note, 19.5% of patients in the control group underwent coronary angiography for STEMIs compared to 14.6% of patients in the intervention group. Moreover, the intervention group had higher incidences of patients with non–STEMI (35.6% vs 33%) and unstable angina (15.3% vs 13.4%) compared to the control group.

The authors demonstrated a reduction in CA-AKI incidence to 7.2% during the intervention period from 8.6% during the control period (time-adjusted OR accounting for clustering, 0.72; 95% CI, 0.56 to 0.93; P =0 .01).

There were no significant between-group differences in major adverse cardiovascular events (28.6% in the intervention group vs 31.5% in the control group; time- adjusted OR, 0.96; 95% CI, 0.83 to 1.12; P=0.63) or major adverse kidney events (9.4% and 11.2%, respectively; time-adjusted OR, 0.89; 95% CI, 0.72 to 1.10; P=0.29). Moreover, there were no significant differences in the number of days patients spent in hospital within 30 days after a procedure in the intervention group (median 2.5 days [IQR, 1.1 to 8.1 days]) compared to the control group (median 2.9 days [IQR, 1.1 to 8.0 days]).

The trial demonstrated a reduction in mean intra-arterial contrast volume administered to 93.1 mL (SD, 61.2 mL) during the intervention period from 112.7 mL (SD, 67.7 mL) during the control period. Moreover, the proportion of cases exceeding the safe contrast volume target was reduced to 38.1% from 51.7%, (time-adjusted OR, 0.77; 95% CI, 0.65 to 0.91; P=0.002).

The mean volume of intravenous crystalloid administered increased to 851.4 mL (SD, 596.4 mL) during the intervention period from 650.0 mL (467.4 mL) during the control period. This was accompanied by a reduction in the proportion of patients who received less than the recommended haemodynamic-guided intravenous fluid volume target; 60.8% in the intervention group compared to 75.1% in the control group (time-adjusted OR, 0.68; 95% CI, 0.53 to 0.87; P=0.002).

The effect of the intervention on the incidence of AKI was consistently observed in subgroups defined by age, sex, presence or absence of heart failure or chronic kidney

disease, at moderate or high risk of AKI, and in those who underwent coronary angiography alone or procedures including PCI as well as when alternate serum creatinine-based definitions for AKI were examined.

In a post hoc analysis, the results remained consistent after excluding data from the 3 physicians who retired before receiving the intervention.

Critique

This trial demonstrated that a clinical decision support system, accompanied by educational outreach, audit, and feedback provided to invasive cardiologists, reduced the incidence of CA-AKI in patients undergoing coronary angiography, percutaneous coronary intervention, or both.

The study authors investigated an important clinical outcome with profound health and socio-economic implications. They provide a robust argument for the need to prevent the development of CA-AKI, which is common, costly, and importantly, modifiable. The primary outcome 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.

The nature of the intervention is a major strength of this study. The educational outreach sessions served to establish clinician trust and achieve optimal compliance. Moreover, a culture of accountability was established with the provision of audit and feedback. The clinical decision support system provided recommendations for a safe contrast volume and haemodynamic-guided intravenous fluid targets, both of which are important mechanisms for reducing the incidence of CA-AKI. Furthermore, in an attempt to enhance compliance with the intervention, physicians were provided with a graphic display of safe contrast volume targets and regular prompts from the catheterisation laboratory staff before the procedure and again when the safe contrast volume target had been reached.

Importantly, the inclusion of all eligible invasive cardiologists in the provincial health system evaluated the effect of the intervention within different cardiac catheterisation units, which serves to enhance the generalisability of the results.

Moreover, the investigators assessed the effect of the study intervention on process-of-care outcomes, which can help aid understanding of the clinical outcomes observed in the study.

Contrast RISK has several important limitations. The trial included a relatively small number of invasive cardiologists working in one region, which limits the generalisability of the results to cardiologists outside this region. Moreover, despite the baseline characteristics being similar between groups, the authors have not reported on race and ethnicity.

Of note, the authors advise that patients undergoing emergency primary PCI for STEMI are excluded due to the time-sensitive nature of the revascularisation process. However, the baseline characteristics clearly describe 630 patients (14.6%) in the intervention group and 681 patients (19.5%) in the control group who underwent an invasive cardiac procedure on the basis of having a STEMI. The reason for this discrepancy is unclear.
Of the 7820 procedures included in this study, 794 (10.2%) were missing data for the primary outcome as serum creatinine levels were not measured during follow-up. Similarly, 698 (8.9%) were missing data on contrast volume. Missing data were handled by multiple imputation methods.

Due to the stepped wedge cluster design, this trial is vulnerable to contamination such that physicians who had not yet received the intervention were aware of the trial and changed their behaviours before receiving the intervention. This would be expected to attenuate the effect of the intervention, suggesting that the treatment effect observed in the trial may be a conservative estimate of the effect of the intervention.

Finally, due to the multi-component design of the study intervention, it is unclear which individual element of the intervention contributed most to the risk reduction.

Contrast RISK highlights that a clinical decision support system combined with educational outreach and audit and feedback reduced the incidence of CA-AKI in patients undergoing cardiac catheterisation. Ultimately, this study is reassuring and encouraging as to the efficacy of clinical decision support in this setting.

This study demonstrates how multicomponent interventions based on predictive risk models can successfully be designed and implemented, and highlights the potential for clinical decision support to be utilised across a range of healthcare settings.

Body of Evidence

A range of interventions have been investigatedUbuntu in an attempt to reduce the incidence of CA-AKI. The AMACING trial[10] was a single-centre prospective randomised, phase 3, controlled, open-label, non-inferiority trial which compared prophylactic hydration with no prophylaxis in a high-risk patient group. The prophylactic hydration group (n=328) received a mean of 1,637 ml (SD 950) of 0.9% normal saline. The control

group (n=332) received no prophylactic hydration. The primary endpoint was the incidence of CA-AKI in each group. There was no difference in the primary outcome, 2.7% (n=8) vs. 2.6% (n=8) in the hydrated vs. non-hydrated groups, respectively (absolute difference, -0.1%; one-sided 95% CI, -2.25 to 2.06; one-tailed P=0.47).

The HYDRAREA trial[11] was a prospective, double-blind, randomised controlled study conducted in 3 French ICUs. HYDRAREA compared 0.9% saline and 1.4% sodium bicarbonate hydration regimens in critically ill patients who received intravascular contrast media. The primary endpoint was the development of CA-AKI 72 hours following contrast exposure. There was no difference between the groups for this outcome (33.3% NaCl vs. 35.1% NaHCO3; adjusted relative risk, -1.8%; 95% CI, -12.3 to 8.9; P=0.81). Nor was there a difference in need for renal replacement therapy, length of ICU stay or mortality.

Technological advancement has contributed to a digital transformation which has allowed electronic health records to guide real-time physician practice in the form of clinical decision support. A large body of evidence has highlighted the efficacy of clinical decision support systems. A systematic review by Kawamoto and colleagues focused on identifying individual features of clinical decision support systems which lead to improvements in clinical practice.[12] The review consisted of seventy studies and utilised multiple logistic regression analysis to identify four features as independent predictors of improved clinical practice. These features included automatic provision of decision support as part of clinician workflow (adjusted OR, 112.1; 95% CI, 12.9- ∞, P<0.00001), provision of recommendations rather than just assessments (adjusted OR, 15.4; 95% CI, 1.3 to 45.6; P=0.0187), provision of decision support at the time and location of decision making (adjusted OR, 15.4; 95% CI, 1.3 to 300.61; P=0.0263), and computer-based decision support (adjusted OR, 6.3; 95% CI, 1.2 to 45, P=0.0294). Contrast RISK successfully employed these features.

The effectiveness of multicomponent interventions in reducing CA-AKI has been previously demonstrated. A prospective multicentre quality improvement study involving 21067 patients undergoing PCI demonstrated that interventions such as standardised hydration orders, reduction of fasting times, pre-intervention fluid bolus therapy, limiting contrast volume, and patient education about self-hydration using oral fluids was encouraged.[9] This study demonstrated impressive results with rates of CI-AKI significantly reduced in hospitals receiving the intervention by 21% (risk ratio, 0.79; 95% CI, 0.67 to 0.93; P=0.005) for all patients and by 28% in patients with baseline estimated glomerular filtration rate <60 mL/min per 1.73 m2 (risk ratio, 0.72; 95% CI, 0.56 to 0.91; P=0.007).

A single-centre study conducted at a US centre demonstrated that the introduction of a mandatory time-out protocol and a discussion regarding the predicted preprocedural AKI risk and the safe contrast limit led to a mean reduction in contrast volume of 55 mL among 3377 patients.[13] Moreover, this study reported an increased odds of AKI when the safe contrast volume limit was exceeded (OR ,1.95; 95% CI, 1.41 to 2.69).

The successful implementation of a personalised contrast volume regimen in patients high risk for AKI undergoing PCI has been demonstrated by Malik and colleagues.[14] Using the National Cardiovascular Data Registry AKI risk model, the investigators developed a novel strategy to define safe contrast limits by entering a contrast term into the model and using it to meet specific relative risk reductions. In 141,133 patients the rate of AKI was 10.0% when the contrast thresholds derived from the model were met compared with 18.2% when they were exceeded (P<0.001).

The effectiveness of personalised haemodynamic guided intravenous fluid strategies in patients undergoing coronary angiography has previously been demonstrated. The POSEIDON[15] randomised controlled trial was a single-centre parallel-group, comparator-controlled, single-blind phase 3 trial which investigated the efficacy of personalised intravenous fluid regimens tailored to left ventricular end-diastolic pressure for the prevention of contrast-induced acute kidney injury in patients undergoing cardiac catheterisation.196 patients were allocated to the left ventricular end-diastolic pressure-guided volume expansion group and 200 were allocated to the control group which received a standard fluid administration protocol. Contrast-induced acute kidney injury occurred less frequently in patients in the left ventricular end-diastolic pressure-guided group (6.7% [12/178]) than in the control group (16.3% [28/172]; RR, 0.41, 95% CI, 0.22 to 0.79; P=0.005).

Other haemodynamic variables have proved beneficial in guiding fluid therapy. A prospective, randomised, double-blind, comparative clinical trial by Qian and colleagues investigated central venous pressure (CVP) guided hydration in patients with chronic kidney disease and congestive heart failure undergoing coronary procedures.[16] 132 patients were in the CVP guided hydration group and 132 patients were in the standard hydration group. Patients in the CVP guided group received a higher volume of fluid (mean 1,827 ± 497 ml vs. 1,202 ± 247 ml; P<0.001) and CA-AKI occurred less frequently in the CVP-guided hydration group than the control group (15.9% vs. 29.5%; P=0.006).

Should we use a combination of educational outreach, clinical decision support with audit and feedback to reduce the incidence of CA-AKI in patients undergoing coronary angiography?

Not yet. Although this multi-faceted intervention reduces the incidence of CA-AKI in patients at risk of AKI, larger trials should be conducted to investigate this strategy and further work is required to ascertain the effect of the intervention in patients undergoing emergency primary PCI.

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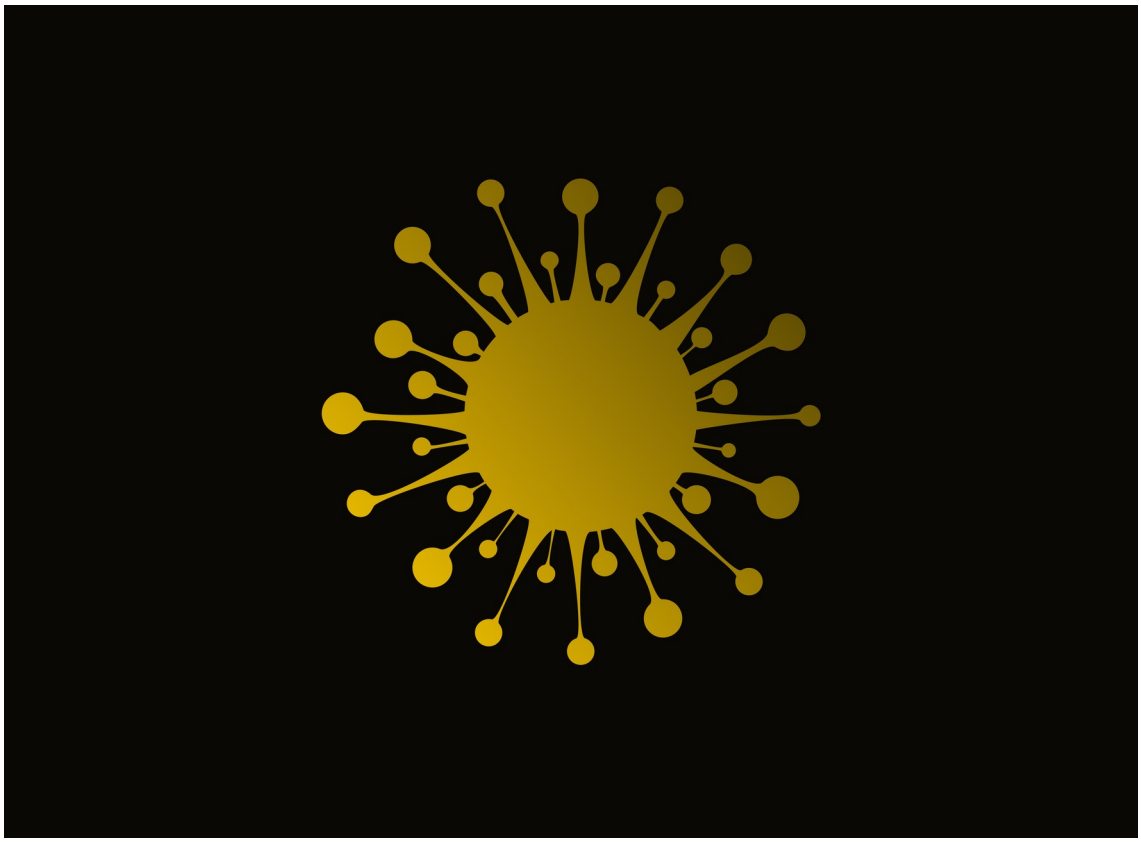

Sepsis Trials

CLASSIC

Meyhoff TS, Hjortrup PB, Wetterslev J, Sivapalan P, Laake JH, Cronhjort M et al. Restriction of Intravenous Fluid in ICU Patients with Septic Shock. N Engl J Med 2022;386(26):2459-2470

Introduction

In 2017, it was estimated there were 48.9 million episodes of sepsis and 11 million sepsis-related deaths.[1] Remarkable, this accounted for almost 1 in 5 deaths globally. One the mainstays of sepsis resuscitation has been the administration of intravenous fluids. This approach has its foundations in the cholera epidemics of the 1800s.[2] While cholera induces severe diarrhoea and resulting fluid loss, sepsis is not typically associated with gross fluid loss.

In 2001 Emanuel Rivers promoted the early-goal directed approach to sepsis management, which involved the administration of vast quantities of fluid. In his paper "Early Goal-Directed Therapy in the Treatment of Severe Sepsis and Septic Shock",[3] both intervention and control arms had received 13,000 ml of intravenous fluid by 72 hours. A triumvirate of trials from the UK,[4–6] Australia & America subsequently refuted the Rivers paper and began the process of moving clinical practice back from a fluid heavy approach. In 2013 Maitland and colleagues[7] published the landmark FEAST trial, and reported harm from fluid bolus therapy in African children with febrile-associated hypotension, when compared to no fluid bolus therapy. Despite a clear signal of harm in a robust randomised controlled trial, it was almost another further decade before a fluid restrictive approach was tested. The Thai CENSER trial[8] compared early low-dose noradrenaline with standard care in 310 adults with sepsis with hypotension. The intervention resulted in higher rate of shock control at 6 hours post randomisation (76.1% vs 48.4%; P<0.001) and a numerically lower 28-day mortality rate (15.5% vs 21.9%).

With evidence suggesting harm from fluid bolus therapy in sepsis and benefit from an early noradrenaline / fluid sparing approach, there was momentum to test a fluid restrictive approach to the resuscitation of patients with sepsis.

Synopsis

CLASSIC (The Conservative vs. Liberal Approach to Fluid Therapy of Septic Shock in Intensive Care Trial) was an international, open-label, stratified, parallel-group, randomised clinical trial with the objective of exploring the effects of restrictive versus standard intravenous fluid therapy on 90-day mortality in ICU patients experiencing septic shock. It ran from November, 2018, to November, 2021, in 31 ICUs in Denmark, Norway, Sweden, Switzerland, Italy, Czech Republic, the UK, and Belgium. Financial support was provided by the Novo Nordisk Foundation.

The study population comprised of individuals aged 18 years or older, with a diagnosis septic shock, which was characterised by suspected or confirmed infection, plasma lactate levels ≥2 mmol/L, an ongoing vasopressor or inotropic agent infusion, and the reception of ≥1 L of intravenous fluids within the 24 hours preceding screening. Exclusion criteria included conditions such as septic shock persisting for more than 12 hours and life-threatening haemorrhage.

The trial employed a centralised, computer-generated allocation sequence for patient randomisation and allocation, with stratification by trial site and the presence or absence of metastatic or haematologic cancer. Patients were randomly assigned in a 1:1 ratio to receive either restrictive or standard intravenous fluid therapy, with permuted blocks of 6 or 8 ensuring balance.

During the trial, patients were allocated to either the restrictive or the standard intravenous fluid therapy group, with the designated intervention applied throughout their ICU stay, potentially up to 90 days. The intervention protocol was resumed if a patient was readmitted to an ICU participating in the trial within the 90-day window. Other therapeutic approaches, such as diuretic usage, were left to the clinical judgement of the managing clinicians.

In the restrictive-fluid cohort, intravenous fluid administration was permitted only under four specific conditions: severe hypoperfusion, documented fluid losses, dehydration or electrolyte deficiency when the enteral route was contraindicated, and ensuring total daily fluid intake of 1 litre when the enteral route was contraindicated.

Conversely, in the standard-fluid group, there was no predefined upper limit for intravenous fluid administration. Fluids could be administered in cases of haemodynamic improvement, fluid replacement or correction of dehydration or electrolyte imbalances, and as maintenance fluid if recommended by the ICU protocol.

Both patient groups were authorised to receive enteral and oral fluids, nutrition (either enteral or parenteral), and fluid used as a medium for medication administration. The protocol also recommended the types of fluids to be administered and concomitant interventions for septic shock, including relevant antibiotic agents, noradrenaline as a vasopressor, and renal replacement therapy based on conservative criteria.

The primary outcome was death within 90 days after randomisation. A sample size of 1554 patients was required to identify an absolute between-group difference of 7 percentage points in 90-day mortality at a two-sided alpha level of 0.05 with 80% power. The trial conduct and patient safety were supervised by the Collaboration for Research in Intensive Care in Copenhagen and an independent data and safety monitoring committee. Interim analyses were performed when 10%, 30%, and 50% of the total enrolled population had been followed for 30 and 90 days, respectively.

2223 patients were screened, 669 excluded, 1554 were randomised, 770 to the restrictive-fluid group and 784 to the standard-fluid group. 764 & 781 were included in the primary analysis, respectively. The most common reasons for exclusion were prolonged septic shock and lack of consent.

The baseline characteristics of the two groups were found to be largely similar, although there were fewer patients with pulmonary infections in the trial groups compared to the general population of patients in the participating intensive care units (ICUs). The median age of the cohort was 70 years, 59% were male, and 46% had chronic hypertension. The median time from ICU admission to randomisation was 3 hours. 75% came from either the emergency department or hospital ward. The predominant site of infection was the abdomen (37%), followed by the lungs (27%) and urinary tract (16%). The highest plasma lactate was 3.8 mmol/L, median highest dose of noradrenaline 0.25 mcg/kg/min and median volume of fluids in the 24 hours before randomisation ~3100. Groups were largely similar at baseline.

After 24 hours, the median volume of intravenous fluid was 500 ml and 1313 ml, in the restrictive- and standard-fluid groups respectively. Total fluid volume at this time-point was 1843 and 2708 ml, respectively. At 5 days post randomisation these volumes were 1450 & 3077 and 8864 & 10800, respectively. Median cumulative fluid balances at days 1 and 5 were 725 & 1342 and 1676 & 2420, respectively.

The median length of stay in the ICU for patients in both groups was 5 days post-randomisation, with a spread of 3 to 9 days in the restrictive-fluid group and 3 to 10 days in the standard-fluid group. In both groups, some patients had their intravenous fluid

protocols discontinued while still in the ICU - 10.4% (80 out of 770) in the restrictive-fluid group and 6.5% (51 out of 784) in the standard-fluid group.

At day 90, mortality rates in the two groups were very similar, with 42.3% (323 out of 764) in the restrictive-fluid group and 42.1% (329 out of 781) in the standard-fluid group (difference, 0.1%; 95% CI, –4.7 to 4.9; P=0.96). These results remained consistent even after adjusting for risk factors at baseline and were also in line with the results of the per-protocol analysis. No significant heterogeneity in the intervention effect on mortality at 90 days was found in the pre-defined subgroup analyses.

Serious adverse events occurred in 29.4% (221 out of 751) patients in the restrictive-fluid group and 30.8% (238 out of 772) patients in the standard-fluid group by 90 days post-randomisation, with an adjusted absolute difference of -1.7 percentage points (99% CI, –7.7 to 4.3). Following the administration of intravenous crystalloid fluids, serious adverse reactions occurred in 4.1% of patients in both groups (31 out of 755 in the restrictive-fluid group and 32 out of 776 in the standard-fluid group), with an adjusted absolute difference of -0.1 percentage points (99% CI, –2.8 to 2.6). Lastly, the number of days alive without life support and the number of days alive and out of the hospital at 90 days were found to be similar in the two groups.

Critique

CLASSIC is a landmark trial in the history of sepsis management and is another step along the path towards understanding the complex interplay between fluid administration and outcomes in this infectious syndrome. As an international trial in 31 ICUs across 8 European countries, CLASSIC is certainly generalisable throughout similar healthcare systems.

The protocolised nature of fluid administration in both arms strengthens the trial design and allowed the intervention to be rigorously assessed. The absence of an upper limit in the standard-fluids permitted a greater degree of separation to be achieved between groups. However, this was offset by the requirement that the standard-fluid group could only receive fluids under one of three conditions: a positive haemodynamic response to resuscitation fluids, a requirement to replace expected or observed fluid losses or electrolyte abnormalities, or maintenance fluids if that ICU usually used them. As such, both groups had restrictions on when they could receive fluids, which likely contributed to the narrower difference between groups.

The restrictive nature of the intervention group was impressive, with fluid infusion only permitted if hypoperfusion was present (plasma lactate > 4 mmol/L, mean arterial pressure < 50 mm Hg despite a vasopressor or inotrope, mottling beyond the kneecap),

oliguria of <0.1 ml/kg/hr in the first 2 hours, to replace fluid losses and to correct dehydration or electrolyte abnormalities in the setting of a non-functioning gastrointestinal tract tract. Such a requirement ensured patients were protected from inadvertent fluids.

Consistent with this, a key finding in the trial is the smaller-than-expected degree of separation between the two groups, which is probably reflective of a general move towards "drier" practice internationally.[9] CLASSIC has the feel of a dry versus extra-dry trial, which makes it harder to show a difference in outcomes. Could a median difference of just 2000 ml at 24 hours be expected to alter mortality by the 7% aimed for? Without being critical of the trialists, this is why science is an iterative process. CLASSIC brings us a step further along the road of understanding the syndrome of sepsis. The next steps will be taken by the likes of FLUIDS-ARISE and further advances will be based on all of these, just as we have done with Latta,[2] Rivers,[3] Maitland[7] and a myriad more.

Body of Evidence

Rivers conducted a single-centre, randomised trial to investigate the benefits of early goal-directed therapy (EGDT), largely driven by $ScvO_2$ monitoring, in patients presenting to an emergency department with severe sepsis or septic shock.[3] The intervention group received six hours of EGDT before being admitted to the ICU. The control group received the same care but without the $ScvO_2$ monitoring. To ensure impartiality, clinicians who cared for the patients in the ICU were unaware of the patients' group assignments. The study enrolled 263 patients, with 130 assigned to EGDT and 133 to standard therapy. The baseline characteristics of the two groups were comparable. The results demonstrated that EGDT led to a significant reduction in in-hospital mortality (30.5%) compared to standard therapy (46.5%) ($P=0.009$). From 7 to 72 hours post-intervention, patients in the EGDT group displayed improved physiological parameters, including a higher mean central venous oxygen saturation, a lower lactate concentration, a lower base deficit, and a higher pH, compared to those in the standard therapy group ($P\leq0.02$ for all comparisons). Additionally, patients in the EGDT group had significantly lower APACHE II scores, indicating less severe organ dysfunction, compared to those in the standard therapy group (13.0 ± 6.3 vs. 15.9 ± 6.4, $P<0.001$).

The Fluid Expansion As Supportive Therapy (FEAST) trial[7] examined whether fluid boluses improved the outcomes of children in sub-Saharan Africa who had severe infection and impaired perfusion. 3141 children were randomised into three groups: one group received a bolus of 20 to 40 ml/kg of 5% albumin solution (n = 1050), the second group received a bolus of 20 to 40 ml/kg of 0.9% saline solution (n = 1047), and the third control group received no bolus (n = 1044). The primary outcome was death from any cause at 48 hours. The was halted early after a sign of harm was identified in the fluid

bolus group. Mortality was 10.6% in the albumin-bolus group, 10.5% in the saline-bolus group, and 7.3% in the control group. Fluid boluses significantly increased the risk of death (RR in the bolus groups compared to control, 1.45; 95% CI, 1.13 to 1.86; P<0.001). The increased mortality risk was consistent across various prespecified subgroups and was evident within 8 hours after randomization.

ANDROMEDA-SHOCK[10] was a multi-centre, randomized trial conducted at 28 ICUs in 5 countries. 424 patients with septic shock were assigned to either a resuscitation protocol targeting normalization of capillary refill time (n=212) or one targeting normalizing or decreasing lactate levels at rates greater than 20% per 2 hours (n=212) for 8 hours. The primary outcome was all-cause mortality at 28 days. At day 28, 34.9% of patients in the peripheral perfusion group and 43.4% in the lactate group had died (HR, 0.75; 95% CI, 0.55 to 1.02; P=0.06; risk difference, -8.5%; 95% CI, -18.2% to 1.2%). Peripheral perfusion-targeted resuscitation was associated with less organ dysfunction at 72 hours. No significant differences were observed in the other six secondary outcomes, and no protocol-related serious adverse reactions were confirmed. The study concluded that targeting normalization of capillary refill time did not reduce all-cause 28-day mortality compared to targeting serum lactate levels in septic shock patients, although this dichotomisation based on the P value is probably the incorrect interpretation.

In a randomised clinical trial conducted by Andrews et al,[11] 212 Zambian adults with sepsis and hypotension were assigned to either an early resuscitation protocol (n=107) or usual care (n=105). The primary outcome was in-hospital mortality. In-hospital mortality occurred in 48.1% (51 of 106) of patients in the sepsis protocol group compared to 33.0% (34 of 103) in the usual care group (between-group difference, 15.1%; 95% CI, 2.0% to 28.3%; RR, 1.46; 95% CI, 1.04 to 2.05; P=0.03). In the first 6 hours, patients in the sepsis protocol group received a median of 3.5 L of intravenous fluid, while those in the usual care group received 2.0 L. Vasopressors were administered to 14.2% of the sepsis protocol group and 1.9% of the usual care group. The study concluded that, among adults with sepsis and hypotension in a resource-limited setting, an early resuscitation protocol involving intravenous fluids and vasopressors increased in-hospital mortality compared to usual care. Almost 90% of patients in the trial were positive for human immunodeficiency virus. Further research is needed to understand the effects of these interventions in different low- and middle-income clinical settings and patient populations.

Hjortrup et al[12] conducted the pilot CLASSIC randomized trial involving 151 adult patients with septic shock across nine Scandinavian ICUs, and found that a fluid restriction protocol significantly reduced resuscitation fluid volumes at day 5 and during

ICU stay compared to standard care (mean differences of -1.2 L; 95% CI -2.0 to -0.4; P<0.001 and -1.4 L (-2.4 to -0.4), respectively; p < 0.001). While total fluid inputs and balances did not differ significantly between the groups, the fluid restriction group had fewer cases of worsening acute kidney injury (27/73 vs. 39/72; OR 0.46; 95% CI 0.23 to 0.92; P=0.03) and a lower 90-day mortality rate (25/75 vs. 31/76; OR 0.71; 95% CI 0.36-1.40; P=0.32). The trial was not powered to show differences in these exploratory outcomes, but results suggested potential benefits with fluid restriction in ICU patients with septic shock.

CENSER[8] was a phase II trial, randomised, double-blind, placebo-controlled clinical trial investigating if low-dose noradrenaline administered early in adults with sepsis-induced hypotension could increase shock control within 6 hours compared to standard care. 310 adults were randomly allocated to an early noradrenaline group and a standard treatment group (155 patients in each). The median time from arrival at the emergency room to administering norepinephrine was notably less in the early norepinephrine group (93 min) compared to the standard treatment group (192 min) (P < 0.001). Patients receiving early noradrenaline had a higher rate of shock control within 6 hours (76.1% vs 48.4%; P<0.001). No significant difference was observed in the 28-day mortality rate between the early norepinephrine group (15.5% vs 21.9%; P = 0.15).
However, the early noradrenaline group was linked with lower occurrences of cardiogenic pulmonary oedema (14.4% vs 27.7%; P=0.004) and new-onset arrhythmia (11% vs 20%; P=0.03).

The CLOVERS (Crystalloid Liberal or Vasopressors Early Resuscitation in Sepsis) trial was a multi-centre, randomised, unblinded superiority trial conducted across 60 US centres from March 2018 to January 2022. The trial examined the impact of early vasopressor administration in patients with sepsis-induced hypotension, comparing a restrictive fluid strategy (with early vasopressor usage) to a liberal fluid strategy. The primary clinical question was whether the restrictive fluid strategy resulted in lower mortality before discharge by day 90 compared to the liberal fluid strategy. The trial included adult patients with suspected or confirmed infection and sepsis-induced hypotension, defined as a systolic blood pressure less than 100 mm Hg or mean arterial pressure (MAP) less than 65 mm Hg following more than 1000 ml IV fluid. The trial excluded patients who had more than 4 hours since meeting the inclusion criteria for sepsis-induced hypotension, more than 24 hours since hospital presentation, or more than 3000 ml (including pre-hospital). In total, 1563 patients were randomized, with 782 assigned to the restrictive group and 781 to the liberal group. The early vasopressor group received ~ 2134 ml less fluid than the liberal fluid strategy at 24 hours, which was permitted by a greater vasopressor use. The trial's primary outcome was death before discharge by day 90. The restrictive group had a mortality rate of 14.0%, while the liberal group had a

mortality rate of 14.9% (difference, -0.9%; 95% CI -4.4 to 2.6; P=0.61). There were no significant differences in secondary outcomes or subgroup analyses.

A prospective, multi-centre, observational cohort study in 17 Finnish ICUs involving 296 critically ill patients receiving renal replacement therapy (RRT) found that fluid overload (cumulative fluid accumulation >10% of baseline weight) at RRT initiation was associated with a higher 90-day mortality rate.[13] The crude 90-day mortality for patients with fluid overload was 59.2% (45 of 76), compared to 31.4% (65 of 207) for patients without fluid overload (P < 0.001). After adjusting for factors like disease severity, RRT initiation time, initial RRT modality, and sepsis, fluid overload was still associated with a 2.6 times higher risk for 90-day mortality. Among 168 survivors with data on RRT use at 90 days, 18.9% (34 patients) were still dependent on RRT.

A systematic review[14] including 49 studies found that conservative or deresuscitative fluid strategies in adults and children with ARDS, sepsis, or SIRS led to increased ventilator-free days (mean difference 1.82 days, 95% CI 0.53 to -3.10, I^2 = 9%) and reduced ICU stay length (mean difference -1.88 days, 95% CI -0.12 to -3.64, I^2 = 75%) compared to liberal strategies or standard care. However, there was no significant difference in mortality between the groups (pooled risk ratio 0.92, 95% CI 0.82 to 1.02, I^2 = 0%). The effect of fluid strategies on mortality in critically ill patients remains uncertain, highlighting the need for large randomized trials to determine optimal fluid strategies.

A systematic review and meta-analysis[15] of nine randomized clinical trials (n=637) conducted to assess the benefits and harms of lower vs higher fluid volumes in adult patients with sepsis found no significant differences in all-cause mortality (RR, 0.87; 95% CI, 0.69 to 1.10; I^2 = 0%; TSA-adjusted CI, 0.34 to 2.22) or serious adverse events (RR, 0.91; 95% CI, 0.78 to 1.05; I^2 = 0%; TSA-adjusted CI, 0.68 to 1.21). No trials reported on quality of life, and there were no differences found in secondary or exploratory outcomes. The quality of evidence was very low for all outcomes, indicating a lack of strong evidence supporting decisions on the volumes of IV fluid therapy in adults with sepsis.

In a recent systematic review and meta-analysis[16] of eight randomized controlled trials involving 2375 septic patients, a restrictive fluid resuscitation approach following the initial 30 ml/kg resuscitation period did not significantly reduce mortality (37% vs. 40% with usual care; RR 0.90, 95% CI 0.76 to 1.06, P=0.23, I^2 = 24%) or impact rates of acute kidney injury, renal replacement therapy, ICU or hospital length of stay, duration of vasopressor therapy, or incidence of limb/digital ischaemia. However, it did significantly reduce ventilator days (mean difference -1.25 days, 95% CI -1.92 to -0.58 days, P=0.0003,

I^2 = 90%). Larger trials are needed to establish optimal fluid management for septic patients.

Should we routinely restrict fluid administration to critically ill patients in the ICU with septic shock

Potentially yes. The CLASSIC trial provides robust evidence that, in a highly resourced setting, there is little difference in outcome between a very restrictive and a restrictive fluid strategy.

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HELMET-COVID

Arabi YM, Aldekhyl S, Al Qahtani S, Al-Dorzi HM, Abdukahil SA, Al Harbi MK. Effect of Helmet Noninvasive Ventilation vs Usual Respiratory Support on Mortality Among Patients With Acute Hypoxemic Respiratory Failure Due to COVID-19. The HELMET-COVID Randomized Clinical Trial. JAMA 2022;328(11):1063-1072

Introduction

The HELMET-COVID trial aimed to compare the effect of non-invasive ventilation (NIV) delivered by helmet with usual care (NIV delivered by face mask, high-flow nasal oxygen, or face mask oxygen) on mortality in patients with acute hypoxaemic respiratory failure due to COVID-19.

Although non-invasive ventilation has been a treatment for respiratory failure for decades, its application, and thus effectiveness, is often limited by patient discomfort and intolerance of tight-fitting face masks, poor mask fit and impaired delivery of ventilation, and by side effects such as skin breakdown. The use of a helmet interface is intended to improve tolerability and delivery of ventilation, and thus to allow the potential advantages of NIV, such as avoidance of sedative medications and preservation of cough reflexes, to be realised to the benefit of patients. However, measurement (and thus control) of inspiratory and expiratory flow and tidal volume is more difficult than with a mask, and it is possible that this may increase exposure to injurious spontaneous breathing patterns.

During the COVID-19 pandemic, acute hypoxaemic respiratory failure was the most common presentation to hospitals, and healthcare systems faced unprecedented demand to provide supportive care. Intubation and invasive mechanical ventilation are resource-intensive, costly, and, particularly in the context of COVID-19, associated with prolonged stay in intensive care and long-term complications. Thus, a mode of providing non-invasive support and reducing the requirement for intubation and invasive mechanical ventilation could have major implications for patients and for healthcare systems, potentially extending beyond the pandemic period.

Synopsis

The HELMET-COVID trial aimed to investigate whether non-invasive ventilation using a helmet interface was superior to usual care in adults with acute hypoxaemic respiratory failure due to proven or suspected COVID-19.

The trial was an investigator-initiated, multicentre, open-label randomised trial comparing NIV delivered through a helmet interface with usual care (mask NIV, HFNO, or face mask oxygen). The trial ran in eight centres in Saudi Arabia and Kuwait, seven of which had prior experience with helmet NIV, recruiting patients between February and November of 2021.

Patients were included if they were adults (variably defined as over 14, 16 or 18 years of age depending on unit policy), had acute hypoxaemic respiratory failure requiring at least 10L/minute of supplemental oxygen due to suspected or proven COVID-19, and were sufficiently alert to follow commands.

Exclusion criteria included an indication for alternative airway or ventilatory support, for example, a tracheostomy in situ or upper airway obstruction; patients already established on helmet NIV or with a previous intubation on the same hospital admission; decreased level of consciousness (Glasgow coma scale<12) or a do-not-intubate order. Consent from patients or their substitute decision-maker and agreement from the treating clinician was mandatory.

Patients were randomised 1:1 to either helmet NIV or to usual care, stratified by centre. In the intervention group, helmet NIV was initiated as soon as possible, delivered through an ICU ventilator, with initial PEEP of 10 cmH20, FiO2 1.0 and pressure support 8-10 cmH20. Settings were titrated to effect according to a written protocol, based on oxygenation, respiratory rate and accessory muscle use. Dexmedetomidine infusion, but no other sedative agents, could be used to facilitate patient tolerance of helmet NIV. If not tolerated by the patient, usual alternative approaches were used as in the usual care group.

Usual care comprised NIV delivered by mask, HFNO, or face mask oxygen according to usual unit practices. Other interventions were not protocolised, but a written guideline with criteria for intubation was provided for patients in both treatment arms. Criteria included persistent high FiO2 requirement (>70%) or PaO2/FiO2 ratio<100mmHg, haemodynamic instability, and radiologic deterioration as well as respiratory acidosis, tachypnoea and intolerance of mask interface. As in the intervention group, dexmedetomidine infusion, but no other sedative agents, could be used to facilitate patient tolerance of respiratory support.

The primary outcome was 28-day mortality, with secondary outcomes including endotracheal intubation and intensive care, ventilator, vasopressor and renal replacement therapy-free days, as well as adverse events.

Sample size calculation was based on a 40% baseline mortality and an absolute risk reduction of 15% with helmet NIV, informed by published outcome data for COVID-19 and a network meta-analysis investigating helmet NIV in non-COVID-19 populations. Allowing for 5% loss to follow up, and to provide 80% power, a sample size of 320 was planned. Several pre-specified subgroups were planned based on age, severity of hypoxaemia, body mass index, APACHE II score and baseline NIV use.

A total of 659 patients were screened, 322 randomised, and after one patient in each group was excluded post-randomisation due to the need for emergent intubation, 320 were included in the trial, all of whom completed 28-day follow-up. The arms were balanced at baseline and the population typical of studies in COVID-19 with a preponderance of males and a high proportion of patients with obesity, diabetes and cardiac disease.

Compliance with the intervention was good: 156 of 159 patients in the intervention group received helmet NIV for a median of 3 days, only 4 of these for < 1hour. Median time on helmet NIV was 21 and 22 hours on study day 1 and 2 respectively, decreasing thereafter. Only 4 patients in the usual care group crossed over to receive helmet NIV. Of patients who were intubated, intolerance of the helmet interface was given as a reason in only 14 (8.8%), with worsening of one or more respiratory parameters the main reason reported.

In the usual care group, the vast majority (155 of 161) received mask NIV, for a median of 14 hours in the initial 48 hours. Use of dexmedetomidine to facilitate NIV was lower in the control group (25.5%) than in the helmet NIV group (43.4%).

There was no difference in the primary outcome of 28-day mortality, with rates of 27% and 26.1% respectively (relative risk 1.04; 95% CI 0.72 to 1.49). There was also no difference in the rate of any secondary outcome, including the rate of endotracheal intubation (47.2 versus 50.3%; RR 0.94, 95% CI 0.75 to 1.17).

Physiological parameters such as respiratory rate and oxygenation, SOFA scores and patient-reported dyspnoea and discomfort (rated using a visual analogue scale) did not differ between treatment arms.

Pre-specified subgroup analysis (based on age, PaO2/FiO2 ratio, baseline use of mask NIV, BMI, APACHE II score) revealed similar outcomes between treatment arms in all subgroups. In post-hoc subgroup analyses, no treatment effect was evident in centres with higher or lower levels of prior experience with the helmet interface. In a further post-hoc subgroup analysis based on PaCO2 level at baseline, 28-day mortality in the

hypocapnic subgroup was 25.3% compared with 30.5%, RR 0.83 (95% CI 0.50 to 1.37) and for the normocapnic subgroup 28.8% versus 21.5% (RR 1.34, 95% CI 0.78 to 2.30).
180-day outcomes (mortality and health-related quality of life measured using the EQ-5D scale) are to be reported in a separate manuscript.

Adverse event rates were reported per group but no statistical comparisons were performed: barotrauma in 30 (18.9%) versus 25 (15.5%) of patients in the helmet NIV and usual care arms respectively. The incidence of skin pressure damage was 3.1% in the helmet NIV arm and 6.2% in the usual care arm.

Critique

This is a well-conducted trial by an experienced group of trialists, which addressed an important clinical question. The study aimed to be pragmatic, for example in allowing the full range of support options in the usual care arm. However, this was appropriately balanced against the need to avoid one of the pitfalls of pragmatic trials where outcomes are driven in part by clinician beliefs (for example endotracheal intubation). This was accomplished by the use of clinical guidelines for titration of NIV settings and criteria for endotracheal intubation. The inclusion and exclusion criteria were broad and reflected the patient population who might plausibly be expected to benefit from the intervention, and baseline characteristics demonstrate this: predominantly the patients had isolated hypoxaemic respiratory failure with a typical population for COVID-19 pneumonitis requiring intensive care i.e. a preponderance of male, overweight patients with diabetes and cardiac disease. The trial was multicentre, although one centre (King Abdulaziz Medical City, Riyadh) contributed over half of the patients, and there were only 8 centres in total of which 3 enrolled fewer than ten patients. The authors comment that the pressure of the pandemic did not allow for additional, less experienced, centres to participate.

All but one of the centres involved was experienced in the use of helmet NIV, and this is demonstrated by high levels of fidelity with the intervention. Almost all patients in the intervention group received helmet NIV, for a median total duration of 43 hours. Protocol deviations were few, with 4 patients crossing over to receive helmet NIV in the usual care arm. Overall, therefore, fidelity with the trial intervention was remarkably high.

The sample size calculation overestimated baseline mortality (40% estimated versus 26.1% actual 28-day mortality for the usual care group). This is perhaps unsurprising, given the high mortality reported in early series when the study was developed[1,2] and the rapid advances in therapeutics in the period between study design and recruitment. Of note, all patients in the trial received corticosteroids and the majority tocilizumab,

showing good translation of evidence to practice. The estimated absolute risk reduction of 15% was large, but in keeping with previous reports of mortality reduction in other trials investigating helmet NIV.[3] The trial was underpowered to find a mortality reduction – over 1000 patients would have been needed in each arm to provide 80% power to identify a 5% absolute risk reduction in 28-day mortality, for example. The authors rightly comment on this imprecision in the effect size estimate and the potential for clinically important benefit or harm to be missed. However, given the nearly identical mortality in the two arms, and the lack of any difference in intermediate physiological or process outcomes such as oxygenation parameters, respiratory rate, and requirement for endotracheal intubation, it seems relatively unlikely that an important effect was missed.

Reporting of some outcome measures was not particularly informative. For example, fewer than half of the patients in the helmet NIV group received endotracheal intubation, so the reported median ventilator-free days was 28 (IQR 0 to 28). This is not a helpful summary of the near-50% rate of intubation and the duration of mechanical ventilation which followed. 'Days free of respiratory support' may, for example, have been a more useful measure.

The choice of comparator can be seen as both a strength and a weakness of the trial – allowing a nuanced selection of treatment modality by the treating clinician according to dynamic changes in patient condition as well as local practice. However, it does limit direct comparison between helmet NIV and other specific modalities such as HFNO.
Although mask NIV use was near-universal in the usual care arm (155 of 161 patients), the duration of time spent on helmet NIV (median 34 of the first 48 hours) was in marked contrast to that spent on mask NIV (14 of the first 48 hours). Dexmedetomidine use was considerably higher in the helmet NIV arm (43.4% rather than 25.5%), perhaps due to clinicians electing to switch to other modalities (HFNO or face mask oxygen) in preference to initiating dexmedetomidine to facilitate compliance with mask NIV.

The authors' conclusion, 'helmet non-invasive ventilation did not significantly reduce 28-day mortality compared with usual respiratory support among patients with acute hypoxaemic respiratory failure due to COVID-19 pneumonia' is valid. Despite experienced centres, evident safety and good patient tolerance leading to excellent treatment fidelity, helmet NIV did not improve physiological parameters, need for endotracheal intubation or 28-day mortality.

Body of Evidence

Prior to the COVID-19 pandemic, a number of randomised trials compared non-invasive oxygenation strategies in patients with acute hypoxaemic respiratory failure,

summarised in a network meta-analysis by Ferreyro et al.[3] The largest of these compared high flow nasal oxygen with standard facemask oxygen in 776 immunocompromised patients, finding no difference in rates of 28-day mortality or endotracheal intubation.[4]

The largest study of helmet NIV included 209 patients with acute hypoxic respiratory failure after abdominal surgery and randomised patients to CPAP via a helmet device or to oxygen via a standard facemask, finding a lower rate of endotracheal intubation, ICU length of stay and other clinical outcomes.[5] However, in this population it is likely that basal atelectasis was the predominant pathophysiological process, which is very different from COVID-19, and arguably more likely to benefit from helmet CPAP.

The network meta-analysis by Ferreyro et al[3] included comparisons of helmet NIV versus standard oxygen (3 studies, 330 patients), finding a 19% absolute risk reduction in mortality and 32% absolute risk reduction in endotracheal intubation. However, this was dominated by the trial by Squadrone et al[5] described above and due to differences in pathophysiology, this evidence is not directly applicable to COVID-19. Other comparisons with face mask NIV and high-flow nasal oxygen were even less robust, although both strongly favoured helmet NIV.

In the setting of COVID-19, the largest trial comparing modes of supporting oxygenation was the RECOVERY-RS5,[6] in which 1273 patients with hypoxic respiratory failure were randomised to CPAP, HFNO or standard oxygen therapy. In this trial, an initial strategy of CPAP use reduced rates of intubation or 30-day mortality compared with standard oxygen therapy. A helmet interface was not used, and CPAP was delivered by mask.

In the HENIVOT randomised trial,[7] 110 patients with severe hypoxic respiratory failure due to COVID-19 were randomised to receive helmet NIV or HFNO. Although the number of days free of respiratory support, the primary outcome, was greater in the helmet NIV arm by 2 days, this did not reach statistical significance. Rates of endotracheal intubation were lower with helmet NIV (30% versus 51%, absolute risk reduction of 21%, 95% CI -38 to -3%) as was the number of days alive and free of mechanical ventilation at 30 days (median 28 versus 25, mean difference 3 days (95% CI 0-7 days)). For other outcomes, the results favoured helmet NIV although did not reach statistical significance.

In a small, single centre randomised trial[8] comparing a helmet or mask interface for delivery of NIV in 60 patients with hypoxic respiratory failure due to COVID-19, Saxena et al found lower rates of endotracheal intubation and shorter length of ICU and respiratory support with a helmet interface.

In conclusion, the HELMET-COVID trial shows that a helmet interface for NIV is a safe option for the delivery of non-invasive support in hypoxaemic respiratory failure due to COVID-19. The helmet interface is better-tolerated than a mask interface, allowing more prolonged use, and may result in fewer complications. It is perhaps surprising, therefore, that this trial did not result in a reduced need for endotracheal intubation nor improved clinical outcomes for patients with acute hypoxic respiratory failure due to COVID-19. Given the overestimated baseline mortality rate and an optimistic estimated effect size due to extrapolation from quite different populations, however, the trial was underpowered to detect anything other than a very large difference in mortality rates.

The HELMET-COVID trial was included in a recently published updated network meta-analysis comparing approaches to non-invasive respiratory support for acute hypoxic respiratory failure.[9] The authors found that helmet CPAP (moderate certainty) and helmet bilevel NIV as used in the HELMET-COVID trial (low certainty) probably reduce mortality compared with standard oxygen therapy.

Should we use helmet NIV for hypoxic respiratory failure due to COVID-19?

Helmet NIV is a safe and well-tolerated option for non-invasive support for acute hypoxic respiratory failure, including that due to COVID-19, and may be better than mask NIV. However in this trial, which was underpowered, this did not translate into clinical benefit.

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RECOVERY-RS

Perkins GD, Ji C, Connolly BA, Couper K, Lall R, Baillie K, et al. Effect of Noninvasive Respiratory Strategies on Intubation or Mortality Among Patients With Acute Hypoxemic Respiratory Failure and COVID-19. The RECOVERY-RS Randomized Clinical Trial. JAMA 2022;327(6):546-558

Introduction

The novel SARS-CoV-2 virus, responsible for the COVID-19 pandemic, has precipitated an unprecedented global health crisis since its initial detection in Wuhan, China, in December 2019. The virus swiftly spread worldwide, with the World Health Organization declaring a pandemic on March 11, 2020. Within just 3 months, SARS-CoV-2 had spread to 114 countries, with 118,000 known cases and 4,291 deaths.[1]

The clinical spectrum of COVID-19 ranges from asymptomatic infection to severe pneumonia with acute respiratory distress syndrome (ARDS), multi-organ failure, and death. Severe COVID-19 pneumonitis often results in hypoxaemic respiratory failure, necessitating oxygen therapy and, in the most severe cases, mechanical ventilation (Zhou et al., 2020).[2] During the early phase of the pandemic, the optimal approach to respiratory support for patients with COVID-19 was a subject of considerable uncertainty and debate.

The use of invasive mechanical ventilation (IMV) was initially considered the gold standard for managing ARDS patients. However, this approach was associated with high mortality rates and significant resource consumption, and concerns arose about the risk of nosocomial transmission.[3] These factors led to a reevaluation of alternative respiratory support modalities, namely continuous positive airway pressure (CPAP) and high-flow nasal oxygen (HFNO).

Both CPAP and HFNO have been used previously in the management of acute hypoxaemic respiratory failure, each with its unique advantages and limitations.[4] CPAP improves alveolar recruitment, reduces work of breathing, and may prevent the need for intubation. HFNO delivers humidified oxygen at high flow rates, improving oxygenation, reducing respiratory rate, and enhancing patient comfort. However, the role of these non-invasive respiratory support modalities in the context of COVID-19 remained unclear during the early pandemic period due to limited evidence and concerns about

patient-induced lung injury, potential aerosol generation and subsequent viral transmission to healthcare workers.

With a clear evidence gap, ventilatory practices during the pandemic displayed significant variability, underscoring the need for large-scale trials. The RECOVERY group in the UK rapidly organised a platform trial capable of investigating multiple interventions in COVID-19.

Synopsis

The Randomized Evaluation of COVID-19 Therapy–Respiratory Support (RECOVERY-RS) trial was a parallel group, open-label, adaptive, three-group, randomized clinical trial implemented across 48 acute care hospitals in the UK and Jersey. It was designed to evaluate the clinical effectiveness of Continuous Positive Airway Pressure (CPAP) or High-Flow Nasal Oxygen (HFNO), compared with conventional oxygen therapy, in hospitalised patients suffering from acute hypoxaemic respiratory failure due to COVID-19.

Eligible participants were adults (18 years and above) with known or suspected COVID-19 who exhibited acute hypoxaemic respiratory failure, with a recorded oxygen saturation of 94% or less while receiving an inspired oxygen fraction of at least 0.40. Those excluded from the trial were patients requiring immediate invasive mechanical ventilation within an hour, pregnant women, or those for whom treatment withdrawal was planned.

The patients were randomized via an internet-based system, accounting for potential unavailability of CPAP or HFNO at hospital sites, and maintaining allocation ratios within permitted thresholds. The randomisation was stratified by hospital site, sex, and age, generated by a minimisation algorithm.

The methods of treatment were implemented as follows:

1. **Continuous Positive Airway Pressure (CPAP):** The participants who were assigned to the CPAP group commenced their treatment immediately after randomization. The CPAP applied did not allow for the integration of any inspiratory positive airway pressure. The selection of the device, its setup, adjustments of parameters like the fraction of inspired oxygen, flow, and positive end-expiratory pressure, as well as the goals for treatment, such as peripheral oxygen saturation, were determined by both the hospital's established procedures and the discretion of the medical team.

2. **High-Flow Nasal Oxygen (HFNO):** For the HFNO group, treatment began promptly post-randomization, similar to the CPAP group. Participants in this group were given HFNO that was heated and humidified. The selection of the treatment's specifics, including device selection, its setup, the adjustments of parameters, and the point at which to halt the treatment, were all influenced by the hospital's guidelines and the medical team's judgment.
3. **Conventional Oxygen Therapy:** Participants who were randomized to receive conventional oxygen therapy were given oxygen through either a standard face mask or a low-flow nasal cannula.

In all the groups, when it was clinically deemed necessary, a tracheal intubation was performed. The trial defined a scenario where a patient received a treatment that was not initially allocated to them (either CPAP or HFNO) for over six hours, unless used as a transition to tracheal intubation or for end-of-life care, as a "treatment crossover".

The primary outcome was a composite of tracheal intubation or mortality within 30 days of randomisation. Secondary outcomes included individual incidence of tracheal intubation or mortality within 30 days, time to tracheal intubation, duration of invasive mechanical ventilation, time to death, mortality during ICU or hospital stay, admission to the ICU, length of ICU stay, and total hospital stay.

Early data on COVID-19 suggested an anticipated 15% event rate in the conventional oxygen therapy group. With this base rate and assuming a conservative 5% reduction for tracheal intubation or mortality, or an odds ratio of 0.625, a total of 3000 participants were required to achieve a power of 90% and a significance level of 0.05. Due to uncertainties related to COVID-19 and event rates, this number was inflated to 4002 participants.

Statistical analysis included logistic regression models for categorical outcomes, mean or median differences for continuous outcomes, and hazard ratios for time to event analysis. The primary analysis was unadjusted while adjusted secondary analyses used covariates of age, sex, morbid obesity, race and ethnicity, FiO2, respiratory rate, and treatment phases, with the hospital site included as a random effect. An inverse probability weighting method was used for secondary exploratory analysis, correcting bias introduced by treatment crossovers. Cutoff values for the final P value for the primary analysis were calculated to correct for the type I error spent at the interim analyses. Secondary outcomes were exploratory in nature due to potential type I error due to multiple comparisons.

The RECOVERY-RS trial, conducted across 48 acute care hospitals in the UK and Jersey, was prematurely concluded due to a rapid decline in hospitalized COVID-19 patients in the UK. Despite this, the trial managed to randomize 1273 patients between April 6, 2020, and May 3, 2021. These patients were divided into three groups: CPAP (380 patients), HFNO (418 patients), and conventional oxygen therapy (475 patients).
The trial participants were predominantly male (66.3%) and of White race (65.3%), with a mean age of 57.4 years. The median time from the onset of COVID-19 symptoms to randomization was 9 days. The majority of the participants received their allocated intervention: 91.6% in the CPAP group, 91.9% in the HFNO group, and 98.3% in the conventional oxygen therapy group.

In the CPAP group, the initial positive end-expiratory pressure was set at a mean of 8.3 cm H2O. In the HFNO group, the initial flow was set at a mean of 52.4 L/min. Treatment crossover occurred in 17.1% of participants, with the highest rate observed in the conventional oxygen therapy group (23.6%).

The primary composite outcome of tracheal intubation or mortality within 30 days was observed in 36.3% of the CPAP group and 44.4% of the conventional oxygen therapy group, representing an absolute difference of -8% (95% CI, -15% to -1%; P=0.03). In contrast, there was no significant difference in the primary composite outcome between the HFNO group (44.3%) and the conventional oxygen therapy group (45.1%). A post hoc analysis compared the primary outcome in the CPAP and HFNO groups, and found a 10% absolute decrease (34.6% vs 44.3%; 95% CI, -18% to -2%; P=0.02).

Secondary outcomes revealed a significant reduction in the incidence of tracheal intubation within 30 days in the CPAP group compared to the conventional therapy group. However, there was no significant difference in the incidence of mortality within 30 days between these two groups. Neither CPAP nor HFNO significantly reduced mortality in the ICU or in the hospital.

Adverse events were most frequent in the CPAP group (34.2%), followed by the HFNO group (20.6%), and the conventional oxygen therapy group (13.9%). Serious adverse events were rare but were more common in the CPAP group, with four events classified as probably or possibly linked to the trial intervention.

Critique

The trial's design had several strengths and potential weaknesses. On the one hand, the randomization was stratified by site, sex, and age, and allocation concealment was done online, reducing the potential for bias. Furthermore, the trial had a large sample size,

with 1272 patients eventually included in the analysis across 75 UK hospitals, and it ran for a full year from April 2020 to May 2021.

One potential issue was the subjective nature of the decision to intubate, which was not protocolised but was left to the treating teams' discretion, potentially introducing variability and bias into the primary outcome. However, this approach reflects real-world clinical decision-making, enhancing the trial's external validity, and likely captured clinical practice at the time, at least in the UK, if not worldwide.

The open-label nature of the trial could be seen as a limitation, as it potentially introduced performance and detection biases. Clinicians and patients were aware of the allocated treatment, which could influence their decisions and perceptions of outcomes. However, blinding in trials involving mechanical interventions like CPAP or HFNO is challenging, if not impossible, due to the physical nature of the interventions.

A relatively large degree of crossover occurred, mostly from the conventional oxygen group to the CPAP and HFNO groups. About 23.6% of patients crossed over from conventional oxygen to CPAP or HFNO (8.4% to CPAP, 7.6% to HFNO, 7.6% to both). About 15% of patients randomised to CPAP received HFNO and 11.5% of patients randomised to HFNO received CPAP. This crossover potentially strengthens the outcome of the study as the crossover of patients from the conventional oxygen group to CPAP or HFNO groups would bias the results toward null outcome. However, this again reflects the reality of clinical practice, where treatment plans are often adapted based on individual patient responses.

The trial did not reach its initially calculated sample size of 4002 patients, largely due to a decrease in COVID-19 cases, which led to recruitment ceasing at the 12-month point. This could potentially impact the power of the study to detect differences between groups. However, it's worth noting that the analysis still included a substantial number of patients (1272), and significant differences were detected in key outcomes. However, because of the lower sample size, the fragility index of the study is 5, which means that 5 more patients could have potentially changed the outcome from significant to insignificant. There is no threshold number for the fragility index to signify if a trial is robust, but higher numbers are better. Conversely, trials are designed to be fragile, to minimise the number of patients subjected to therapies of uncertain efficacy. A fragility index of 0 means that a significant outcome could become insignificant by using an alternative statistical test. Trials published in well-known journals have had a fragility index of around 8.[5] 13 patients were not included in the final analysis because they either withdrew (8 patients) from the trial or were lost to follow-up (5 patients). With the trial’s fragility index at 5, it raises the theoretical possibility of the trial results

becoming insignificant if these 5 of the patients that were lost to follow up were included in the trial. It is also important to keep in mind the crossovers of patients from CPAP and HFNO arm into the conventional oxygen arm, which could affect this number.

Overall, the RECOVERY RS trial was well-conducted, given the constraints and complexity of conducting clinical trials during a pandemic. It has provided valuable insights into the use of different respiratory support strategies for patients with severe COVID-19.

Body of Evidence

The FLORALI trial[6] was a multi-centre randomized controlled study comparing high-flow oxygen therapy, standard oxygen therapy delivered via a face mask, and non-invasive positive-pressure ventilation in 310 patients with acute hypoxaemic respiratory failure and a ratio of the partial pressure of arterial oxygen to the fraction of inspired oxygen of 300 mm Hg or less, but without hypercapnia. The primary outcome was the rate of intubation at 28 days and occurred at 38% in the high-flow oxygen group, 47% in the standard oxygen group, and 50% in the non-invasive ventilation group, with no statistically significant differences among the groups (P=0.18). However, the high-flow oxygen group had significantly more ventilator-free days at day 28 (24±8 days) compared to the standard oxygen group (22±10 days) and the non-invasive ventilation group (19±12 days) (P=0.02). The hazard ratio for death at 90 days was 2.01 (95% CI, 1.01 to 3.99) with standard oxygen versus high-flow oxygen (P=0.046), and 2.50 (95% CI, 1.31 to 4.78) with non-invasive ventilation versus high-flow oxygen (P=0.006), suggesting a higher risk of death with the standard oxygen and non-invasive ventilation treatments compared to high-flow oxygen therapy.

HENIVOT[7] was a multi-centre, randomised clinical trial conducted across Italian ICUs in Italy. It ran from October to December 2020 and compared the effect of helmet non-invasive ventilation with high-flow nasal oxygen alone 109 patients with COVID-19-induced moderate to severe hypoxaemic respiratory failure (PaO_2 / FiO_2 ≤ 200). Participants were randomly divided into two groups. The helmet NIV group (n=54) received continuous helmet NIV, with a positive end-expiratory pressure of 10-12 cm H_2O and pressure support of 10-12 cm H_2O, for at least 48 hours followed by high-flow nasal oxygen. The HFNO group (n=55) received this modality alone at 60 L/min. There was no significant difference in the primary outcome, the median number of respiratory support-free days by day 28; Helmet-NIV group, 20 days (IQR, 0-25) vs HFNO group,18 days (IQR, 0-22); mean difference, 2 days; 95% CI, −2 to 6; P=0.26. Of the nine pre-specified secondary outcomes reported, seven showed no significant difference. However, the rate of endotracheal intubation was significantly lower in the helmet group (30%) than in the high-flow nasal oxygen group (51%) (difference, −21%; 95% CI,

–38% to –3%; P=0.03). Furthermore, the median number of days free of invasive mechanical ventilation within 28 days was significantly higher in the helmet group (28 vs 25; mean difference, 3 days; 95% CI, 0 to 7; P=0.04). The rate of in-hospital mortality was similar for both groups (24% vs 25%, respectively).

Ferreyro and colleagues[8] completed a systematic review and meta analysis of 25 randomised controlled trials, including 3804 adult patients with acute hypoxaemic respiratory failure, comparing high-flow nasal oxygen, face mask non-invasive ventilation, helmet non-invasive ventilation, or standard oxygen therapy. Compared to standard oxygen, both helmet non-invasive ventilation (RR, 0.40; 95% CrI, 0.24 to 0.63; absolute risk difference, –0.19; 95% CrI, –0.37 to –0.09) and face mask noninvasive ventilation (RR, 0.83; 95% CrI, 0.68 to 0.99; absolute risk difference, –0.06; 95% CrI, –0.15 to –0.01) were associated with a lower risk of mortality.

Should patients suffering with COVID-19 induced respiratory failure be treated with CPAP, HFNO or conventional facemask oxygen?

The RECOVERY-RS trial presents reasonable evidence to support a choice of CPAP over HFNO or facemask oxygen in this setting.

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Paediatric Trials

FIRST-ABC (Step Up)

Ramnarayan P, Richards-Belle A, Drikite L, et al. Effect of High-Flow Nasal Cannula Therapy vs Continuous Positive Airway Pressure Therapy on Liberation From Respiratory Support in Acutely Ill Children Admitted to Pediatric Critical Care Units: A Randomized Clinical Trial. JAMA 2022;328(2):162-172

Introduction

In paediatric patients, especially infants, acute respiratory diseases are the most common indication for intensive care unit (PICU) admission. The PICU community has widely adopted high-flow nasal cannula (HFNC) therapy as the first-line intervention in such patients, with escalation to non-invasive continuous positive airway pressure (NI-CPAP), in patients who fail to respond adequately. The ubiquity of this approach is founded on clinician experience along with the comparative simplicity and improved tolerability of HFNC compared to NI-CPAP. However, there is an absence of clinical trial data to support current practice and concerns that HFNC may be inferior to NI-CPAP in this population.

Both therapies support the respiratory system by providing heated, humidified, oxygen-enriched gas at inspiratory flow rates in excess of peak inspiratory flow, with the aim of correcting hypoxaemia and reducing the work of breathing. Though HFNC can produce positive end expiratory pressure (PEEP), the amount is very variable.[1] Arguably, this component of the therapy is largely controlled by the patient, who may adapt to HFNC by varying the leak produced by mouth opening. PEEP may improve respiratory function by recruiting and retaining smaller airways and alveolar units. NI-CPAP, most commonly via a nasal interface, tends to produce higher and more reliable PEEP, though it is still variable and dependent upon the degree of per-oral leak. The less comfortable NI-CPAP interface, possibly coupled with a greater severity of illness, not infrequently requires sedation. These additional burdens of care have predictable negative sequelae.

Synopsis

This study sought to ascertain if High-Flow Nasal Cannula (HFNC) was not inferior to Non-Invasive Continuous Positive Airway Pressure (NI-CPAP) as a supportive therapy in children admitted to a Paediatric Intensive Care Unit (PICU) due to an acute respiratory illness. The study, funded by the National Institute for Health Research in the UK (NIHR-

UK), was initiated by investigators and managed by the Intensive Care National Audit and Research Centre (ICNARC) Clinical Trials Unit.

The research was conducted in a pragmatic, unblinded, randomised, controlled, and multicentre fashion with parallel groups. It was based on a previous pilot feasibility trial[2] and carried out alongside the mirrored, post-extubation FIRST-ABC STEP-DOWN trial.[3] The study was carried out in 24 PICUs across the UK between August 2019 and November 2021, with findings published in the Journal of the American Medical Association (JAMA) in July 2022.

Inclusion criteria for patients in the trial required all of the following: admission or acceptance for admission to a PICU, an age greater than 36 weeks corrected gestational age and under 16 years, and an assessment by the treating clinician that non-invasive respiratory support was needed for an acute illness.

Patients were excluded from the trial if they met any of the following conditions: need for immediate intubation and invasive ventilation due to severe hypoxia, acidosis and/or respiratory distress, upper airway obstruction, inability to manage airway secretions or recurrent apnoeas, presence of a tracheostomy, HFNC/CPAP treatment for more than 2 hours within the previous 24 hours, home non-invasive ventilation prior to PICU/High Dependency Unit (HDU) admission, untreated air-leak presence (pneumothorax/pneumomediastinum), midfacial/craniofacial anomalies (unrepaired cleft palate, choanal atresia) or recent craniofacial surgery, agreement for 'not for intubation' or other limitation of critical care treatment plan, or prior recruitment to either FIRST-ABC STEP-UP or STEP-DOWN trials.

A concealed, centralised, web or telephone-based system was used for randomisation, which utilised a computer-generated sequence that was stratified by site and age (less than 12 months vs 12 months or older) using block sizes of 2 and 4. Children were randomly assigned in a 1:1 ratio to the two therapies, which commenced as soon as possible post-randomisation.

Both therapies were executed following a strict protocol, with clear initial settings and weaning and treatment failure criteria. For both groups, the fraction of inspired oxygen (FiO2) was adjusted to maintain peripheral oxygen saturation (SpO2) of 92% or higher. Weaning was standardised, and if treatment failure criteria were met, the patient could be switched to the other therapy or receive any other escalation in support.

The primary outcome was the time from randomisation to the start of a 48-hour period during which a participant was free from all respiratory support other than

supplemental oxygen. Secondary outcomes included several measures, including mortality at critical care unit discharge, rate of intubation at 48 hours, durations of critical care unit and acute hospital stay, patient comfort, sedation use during non-invasive respiratory support, and parental stress at or around the time of consent. Data on mortality at 60 and 180 days, as well as quality-of-life and cost-effectiveness outcomes, are being collected and will be reported in the future.

The study power calculation was designed to exclude the non-inferiority margin of a hazard ratio of 0.75 with a 90% probability and a 1-sided type I error rate of 2.5%. This hazard ratio corresponds to approximately a 16-hour increase in median time to liberation. These estimates were based on the pilot feasibility study,[2] necessitating a sample size of 508. However, to account for potential participant drop-out, the sample size was increased to 600. An interim safety analysis was planned to be conducted after the recruitment of the first 300 patients.

Two separate sets of statistical analyses were performed for all outcomes, the first being based on the randomisation group and the second based on those who started the randomised therapy. Both analyses needed to agree to conclude non-inferiority. The primary outcome analyses were carried out using Cox regression to calculate hazard ratios with one-sided 97.5% confidence intervals adjusted for several pre-specified baseline covariates and subgroups.

The primary outcome also underwent a series of sensitivity analyses, including duration of respiratory support, time from randomisation to the start of weaning, time from randomisation to meeting weaning criteria, and the inclusion of patients who did not start any respiratory support.

All secondary outcomes were evaluated for statistical superiority using a standard two-sided significance threshold of 5% and used the same baseline covariates as the primary outcome.

Critique

The striking difference in the length of stay in the Intensive Care Unit (ICU) and the hospital overall, with a shorter duration for the High-Flow Nasal Cannula (HFNC) group, remains unexplained. Interestingly, the choice of statistical measures stands out: the study used means rather than medians. This choice appears counter-intuitive given the anticipated positive skew of length of stay data. Furthermore, the high standard deviations, particularly in comparison to the mean values themselves, are noteworthy.

Based on the published results so far, it seems reasonable to anticipate no significant difference in mortality at 60 and 180 days. However, the outcomes related to quality of life and cost-effectiveness may differ, potentially reflecting the length of stay results. Notably, this trial took place during the first two waves of the COVID-19 pandemic, a significant detail that, surprisingly, is not addressed in the report.

A recent review of HFNC trials involving adult participants, which includes studies conducted both before and during the COVID-19 pandemic, has been published.[4] The review concludes that a reasonably strong body of evidence supports the superiority of HFNC over conventional (low flow) supplemental oxygen therapy. However, the evidence becomes mixed when HFNC is compared with other non-invasive respiratory support modalities. A significant factor influencing this conclusion is the heterogeneity of patients and therapies.

Body of Evidence

This trial is by far the largest to investigate this question to date, and arguably the best designed. Taking its limitations and pragmatism into account, it appears to support the usual practice of an initial trial of HFNC with escalation to NI-CPAP, either intermittently or continuously, in the event of treatment failure. In short, this should be a personalised, adaptive and patient centric approach that relies heavily on clinician experience, with all of the inherent advantages and disadvantages of such a clinical strategy.

Unlike the authors, I do not think any comparisons with the STEP-DOWN study[3] are justified as the clinical situations are non-analogous.

In paediatric patients admitted to ICU for respiratory support in the context of an acute illness, is starting with HFNC inferior to NI-CPAP?

No. This trial suggests these modalities can and should be used interchangeably. It confirms the clinical experience that a trial of HFNC is often effective; can be stepped-up to NI-CPAP; is better tolerated; and such a strategy does not effect patient centred outcomes.

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FIRST ABC – Step Down

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):1555-1565

Introduction

Invasive mechanical ventilation (IMV) is an effective supportive therapy for patients experiencing respiratory failure. However, the associated burdens of care are substantial and directly contribute to short-term, medium-term, and sometimes even long-term morbidity. Consequently, minimising the duration of IMV has been a significant focus of numerous clinical trials in both adult and paediatric populations.

A prevalent strategy to reduce IMV duration involves planned liberation directly onto high-flow nasal cannulae (HFNC) or non-invasive continuous positive airway pressure (NI-CPAP). These less invasive modalities are also frequently employed when patients deteriorate post-liberation from IMV, as an alternative to an immediate return to IMV.

In both adult and paediatric populations, the use of HFNC has seen exponential growth. It's widely regarded as a comfortable treatment option and is easy to administer, particularly since most modern ventilators now offer this modality. However, there are concerns that HFNC may be deployed in situations where merely supplemental oxygen would be equally effective, and that HFNC provides insufficient respiratory support compared to NI-CPAP or non-invasive ventilation (NIV).

Given the absence of trials comparing HFNC to NI-CPAP in the post-IMV paediatric population, the FIRST-ABC group opted to combine their STEP UP trial,[1] which compared HFNC versus NI-CPAP in Paediatric Intensive Care Unit (PICU) admissions requiring support, with a mirrored trial using the identical intervention algorithm, in a cohort of post-IMV paediatric patients.

Synopsis

This study aimed to determine if High Flow Nasal Cannulae (HFNC) is non-inferior to Non-Invasive Continuous Positive Airway Pressure (NI-CPAP) as supportive therapy in children post Invasive Mechanical Ventilation (IMV). The study, funded by the National Institute for Health Research (NIHR-UK), was an investigator-initiated, randomised, controlled, pragmatic, unblinded, multicentre, parallel-group trial. It was built upon a

previous pilot feasibility study[2] and managed by the Intensive Care National Audit and Research Centre (ICNARC) Clinical Trials Unit. The trial took place in 24 Paediatric Intensive Care Units (PICUs) in the UK from August 2019 to May 2020 and was published in the Journal of the American Medical Association in July 2022.

Inclusion criteria required patients to be admitted or accepted for admission to PICU, be older than 36 weeks corrected gestational age and younger than 16 years, and be assessed by the treating clinician to require non-invasive respiratory support within 72 hours of extubation following a period of invasive ventilation. Exclusion criteria ranged from severe health complications such as upper airway obstruction and untreated air-leak to having a tracheostomy in place or previously being recruited to either FIRST-ABC STEP-UP or STEP-DOWN trials.

Randomisation was managed using a concealed, centralised telephone or web-based system and stratified by site and age, with permuted block sizes of 2 and 4. Children were randomised in a 1:1 ratio to the two therapies, which were to commence as soon as possible post-randomisation. Both therapies were protocolised with maximal initial settings and well-defined weaning and treatment failure criteria. The fraction of inspired oxygen (FiO2) was adjusted to maintain a peripheral oxygen saturation (SpO2) of 92% or higher.

The primary outcome was the time from randomisation to the start of a 48-hour period wherein a participant was free from all respiratory support other than supplemental oxygen. Secondary outcomes included critical care unit discharge mortality; intubation rate at 48 hours; lengths of critical care unit and acute hospital stays; patient comfort, evaluated using the COMFORT Behaviour Scale; sedation use during non-invasive respiratory support; and parental stress at the time of consent, measured using the Parental Stressor Scale: Paediatric Intensive Care Unit. Future reports will present data on mortality at 60 and 180 days, as well as quality-of-life and cost-effectiveness outcomes.

The study's power calculation required a sample size of 600 to ensure a 90% probability with a 1-sided type I error rate of 2.5% to rule out the non-inferiority margin of a hazard ratio of 0.75 (corresponding to an approximately 16-hour increase in median time to liberation), based on the pilot feasibility study.[2] For safety, an interim analysis was planned 60-days post the recruitment of the first 300 patients, with stopping criteria being superiority of the primary outcome or a statistically significant difference in 60-day mortality between the two groups.

Two sets of statistical analyses were performed for all outcomes: one based on the randomisation group including all patients who began any form of respiratory support, and the other based on those starting the randomised therapy. Agreement between these analyses was needed to conclude non-inferiority. Patients were censored either at the time of last known respiratory support or at the time of death. Missing baseline covariates were replaced using multivariable imputation with chained equations.
Several sensitivity analyses were planned for the primary outcome, including duration from start of respiratory support to liberation from respiratory support, and time from randomisation to start of weaning. All secondary outcomes were evaluated for statistical superiority using a standard 2-sided significance threshold of 5% and used the same baseline covariates as the primary outcome.

The trial report comprises a series of consort diagrams detailing the progression of the numerous patients through the trial, as seen in Figure 1 of the main text and eFigures 7 and 8 in the supplementary material. There were 3121 patients screened, of which 1397 met the inclusion criteria. Among these, 797 (57%) were excluded. The primary reasons for exclusion were either not being randomised due to timing or clinician decision (451 patients), or meeting one or more exclusion criteria, most frequently (153 patients) due to clinician decision to use Non-Invasive Ventilation (NIV).

From the 1397 eligible patients, 600 were randomised, with 299 allocated to the High Flow Nasal Cannulae (HFNC) group and 301 to the Non-Invasive Continuous Positive Airway Pressure (NI-CPAP) group. Out of these, 272 started HFNC treatment and 252 initiated NI-CPAP. In the HFNC group, 166 (61%) had treatment success, occurring at a median time of 28 hours, while 101 (37%) experienced treatment failure at a median time of 104 hours. Of those who failed, 64 were switched to NI-CPAP, but 25 of these were later intubated. In the NI-CPAP group, 164 (65%) achieved treatment success at a median time of 23 hours, while 85 (34%) encountered treatment failure at a median time of 83 hours. From those who failed, 31 were switched to HFNC, but 7 of these were later intubated.

Despite randomisation, there were noteworthy differences in the baseline characteristics between the two groups. The HFNC group contained more patients aged 28 days or younger (20% vs 14%) and fewer patients within the 181-364 days age range (13% vs 17%). Furthermore, the HFNC group had a higher proportion of patients who received Invasive Mechanical Ventilation (IMV) due to a cardiac cause (29% vs 20%), while having fewer patients who received IMV for bronchiolitis (35% vs 45%). Other measures showed that the groups were well matched. For instance, 76% of patients were under 1 year of age. The median duration of IMV prior to extubation was 88 hours. Following a period of IMV, as expected, 85% of patients had no or only mild respiratory

distress. Sixty-three percent of patients were randomised before extubation, with the remainder evenly split between those randomised within an hour of extubation and those randomised more than an hour after, which was considered a rescue intervention.

It is of note that the HFNC flow rates used showed a significant number of outliers, both significantly above and below the trial's interventional guideline.
Both analyses yielded identical results of superiority for NI-CPAP, with adjusted hazard ratios of 0.83 and 0.82, respectively. This corresponds to a median difference of 8 hours between the groups in the time from randomisation to the start of a 48-hour period during which a participant was free from all respiratory support other than supplemental oxygen.

As for secondary outcomes, there was no difference in the re-intubation rate at 48 hours, in the duration of PICU or hospital stay, or in any of the other pre-specified outcomes. Regarding mortality, the event number was very low; there was no difference in rate at PICU discharge; however, a statistically significant higher rate was observed at 60 and 180 days in the HFNC group, although the confidence intervals are quite wide.

Critique

This trial was meticulously designed, striking a balance between pragmatism and strict protocolisation. It was large by Paediatric Intensive Care Unit (PICU) standards, reflecting the diverse PICU provision across the UK. The rapid rate of recruitment was unexpectedly high and certainly merits separate consideration.

Nonetheless, the study recruited a heterogeneous group of patients, which introduces the confounding factor of significant differences in baseline characteristics. These differences could plausibly explain the results of the primary outcome. Notably, the apparent superiority of Non-Invasive Continuous Positive Airway Pressure (NI-CPAP) could be especially relevant to the very young and cardiac patient populations.

It's also worth noting that the majority of patients were planned to be extubated onto non-invasive respiratory support. The patients who were not planned to receive this support, and thus required rescue intervention, could be more likely to have poorer outcomes with High Flow Nasal Cannulae (HFNC).

Another important factor to consider when interpreting the implications of this trial is that the reintubation rate at 48 hours and the length of stay, secondary outcomes, showed no difference. These outcomes are frequently used as primary or secondary outcome measures and should not be easily dismissed when they contradict the primary

outcome used. The primary outcome, though novel and valuable, could arguably be less than ideal.

The variability in the HFNC flow rates, which were delivered to a significant proportion of patients, is another potential confounder.

A striking difference was observed in the time to treatment failure between the HFNC and NI-CPAP groups: the median time for HFNC was 104 hours, compared to 83 hours for NI-CPAP. This discrepancy raises the possibility that a failure to liberate from HFNC could be a marker of concern that is currently overlooked in clinical assessment. This oversight could delay re-escalation, which has been associated with worse outcomes.
The late mortality signal, though apparent, should be approached with a high degree of caution due to the very low event rate, the differences in baseline characteristics, and the very wide confidence intervals. Given the small number of events, a hypothesis-generating analysis of these cases could offer valuable insights and provide testable hypotheses.

Body of Evidence

This trial is the first trial of its kind in a paediatric population. The results should best be considered as showing a mixed signal. That said, on balance, it suggests that HFNC should be used in the post-extubation setting with greater caution and vigilance and NI-CPAP, either as the primary modality, or intermittently with HFNC maybe beneficial, especially in more vulnerable patients such as the very young, those with cardiac pathology, those that have had prolonged IMV or have neurological pathology. A soft maximal time of HFNC dependency may also be a useful consideration in evolving guidelines.

In paediatric patients who require non-invasive respiratory support post liberation from IMV are HFNC non-inferior to NI-CPAP?

Probably not. This trial suggests that the choice of modality may have a significant impact in specific patients. Furthermore, the prolonged use of / requirement for HFNC in this patient population should be more strongly considered as an indication to re-escalate support early.

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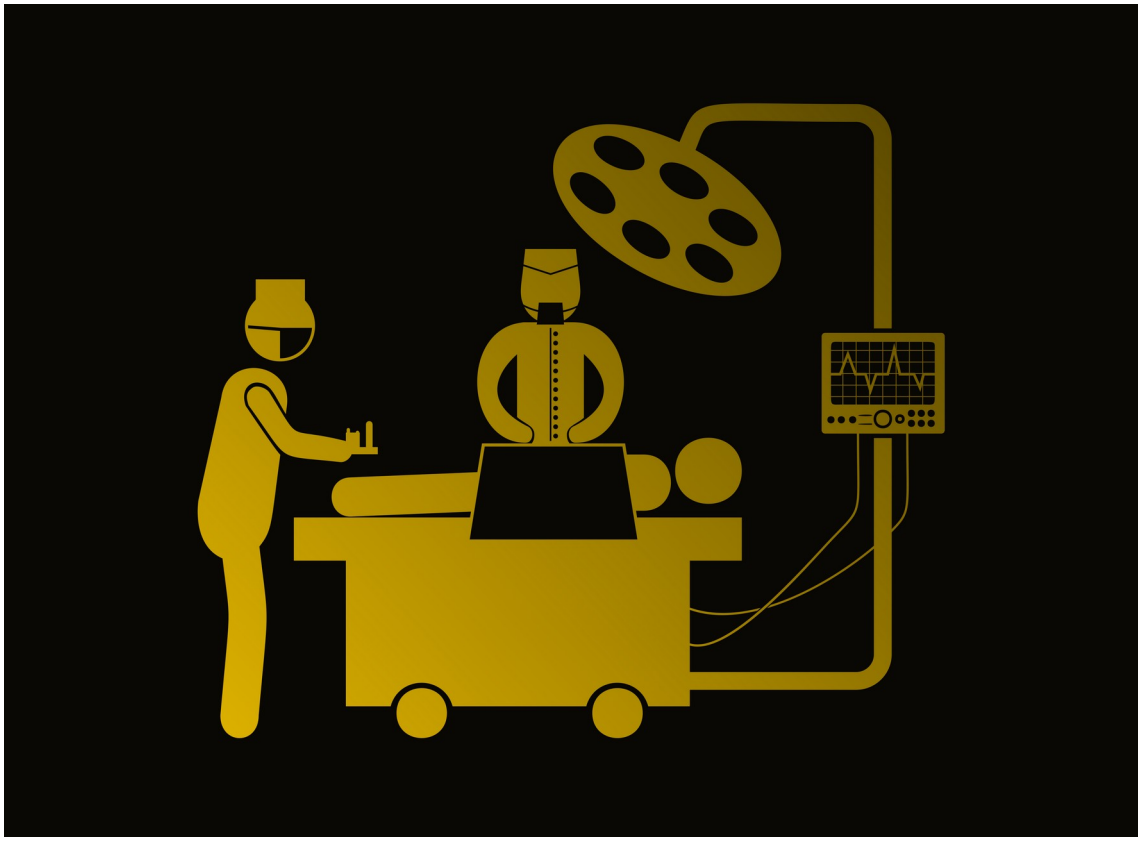

Perioperative Trials

OPTIMAL

Shi J, Zhou C, Pan W, Sun H, Liu S, Feng W, et al. Effect of High- vs Low-Dose Tranexamic Acid Infusion on Need for Red Blood Cell Transfusion and Adverse Events in Patients Undergoing Cardiac Surgery. JAMA 2022;328(4):336

Introduction

One of the main complications of cardiac surgery is excessive bleeding, necessitating blood transfusion and, in the most severe cases, a return to theatre. Methods to try and mitigate against the risk of bleeding in the cardiac population are of the utmost clinical importance as bleeding, blood transfusion and re-operation are all associated with deleterious outcomes and an increased risk of mortality.[1,2] Anti-fibrinolytics, in particular tranexamic acid, are now commonly used to prevent bleeding in patients undergoing cardiac surgery. In the most seminal trial thus far, the ATACAS investigators demonstrated that a bolus of tranexamic acid (TXA) was associated with a lower risk of bleeding, as compared to placebo, without an increased risk of thrombotic complications.[3] TXA use, however, was associated with seizures and consequent stroke and death.[3]

A TXA bolus may not be the most efficacious of administration strategies. It has been demonstrated that a bolus of TXA may be insufficient during prolonged surgeries, and continuous infusion may provide a more stable anti-fibrinolytic profile.[4] Furthermore, an infusion-based strategy may avoid a lower peak concentration and therefore lower the risk of potential adverse events from occurring. The exact dosing required for TXA infusion during cardiac surgery is unknown, with a lack of high-quality randomised controlled trials establishing the effect higher vs lower dose TXA has on postoperative bleeding, thrombotic events and the occurrence of seizures.

The Outcome Impact of Different Tranexamic Acid Regimens in Cardiac Surgery With Cardiopulmonary Bypass (OPTIMAL) trial was designed to compare the effect of a high vs low dose TXA infusion strategy on outcomes in patients undergoing cardiac surgery.[5]

Synopsis

The aim of the OPTIMAL trial was to assess whether a perioperative high dose TXA infusion was associated with a lower requirement of red blood cell transfusion and was non-inferior to a perioperative low dose TXA infusion in respect to thrombotic events,

acute kidney injury and seizures. This was a multi-centre, double-blinded, randomised trial comparing two dosing regimens of TXA in patients undergoing cardiac surgery requiring cardiopulmonary bypass in four cardiac centres in China. Inclusion criteria included patients between the ages of 18-70, awaiting cardiac surgery that required cardiopulmonary bypass, and capable of giving consent. Important exclusion criteria included a previous history of convulsion or seizure, allergy to intravenous TXA, active intravascular coagulation (deep vein thrombosis, pulmonary embolism or arterial thrombosis) or a known thrombophilia. Following stratification by centre, patients were randomised in a 1:1 ratio to a high dose TXA group or a low dose TXA group in permuted blocks of six. The high dose group received a bolus of 30mg/kg after induction of anaesthesia, followed by a maintenance infusion of 16mg/kg/hr with a pump prime dose of 2mg/kg. The low dose group received a bolus of 10mg/kg after anaesthetic induction, followed by an infusion of 2mg/kg/hr with a pump prime dose of 1mg/kg. Clinicians were blinded to the dose, and bolus/ maintenance regimes were administered in the same volume at the same rate for all participants. The doses used were based on previous literature; the high dose regime based on the maximal effective dose of TXA as compared to the low dose regime based on pharmacological data demonstrating the minimally effective dose of TXA.[6,7] Infusions were discontinued at the end of the operation.

The primary efficacy outcome was the proportion of patients requiring any allogenic red cell transfusion between the start of the operation and discharge. Importantly, investigators defined standardised thresholds for transfusion- a Haemoglobin (Hb) <7g/dL during cardiopulmonary bypass, or <8g/dL after bypass. The primary safety outcome was a 30-day incidence of a composite of acute kidney injury (KDIGO stage 2/3), postoperative seizure, thrombotic events (myocardial Infarction, deep vein thrombosis, ischaemic stroke or pulmonary embolism) and all cause mortality. There were various secondary outcomes including the volume of allogenic red blood cell or non-red blood cell transfusion after the start of operation and postoperative bleeding volume. Tertiary outcomes included serum D-dimer levels, volume of cell saver and duration of chest drainage.

It was calculated that for the primary efficacy outcome, 1320 participants would provide 90% power to detect a 7.4% absolute risk reduction and a 28.9% relative risk reduction according to the historical registry data from one of the cardiac centres included in the trial (which had a red cell transfusion rate of 25.5% using a low-dose TXA regime). The estimated risk reduction was based on pilot data carried out by the investigators prior to this study. For the primary safety outcome, the projected 30-day incidence of the safety outcome was 20%, therefore with an absolute non-inferiority margin of 5%, and an assumed 10% dropout rate, 3008 participants would provide 90% to verify the high dose

regimen's non-inferiority to the low dose regimen. Chi-squared tests were used to compare the primary efficacy and safety endpoints between the two groups. T-tests and Chi-squared tests were used for secondary endpoints. Overall, 13,367 patients were assessed for eligibility for inclusion into the trial and of these, 3079 patients were randomised to a treatment group. The majority of patients that were excluded fell out of the target age range (18y-70y) or were undergoing 'off pump' surgery. For those randomised, 98.4% completed the trial. Forty-eight patients were lost to follow-up and therefore excluded from the primary analysis. Groups were well matched at baseline with no discernible differences in baseline physiology or surgical characteristics.
The primary endpoint of allogeneic red cell transfusion occurred in 21.8% of the high-dose group and 26.0% of the low dose group (Relative risk, 0.84 [1-sided 97.55% CI - ∞ to 0.96; p=.004]). Occurrence of the composite primary safety endpoint (seizure, kidney dysfunction, thrombotic events and all-cause mortality) showed equivalence in both arms of the trial, occurring in 17.6% of the high-dose cohort as compared to 16.8% of the low dose cohort (risk difference 0.8%; 1-sided 97.55% CI, –∞ to 3.9%; P = 0.003 for non-inferiority).

Important pre-specified secondary outcomes showed that high dose TXA did not significantly increase the incidence of seizures. Furthermore, there were no statistically significant difference in length of mechanical ventilation, ICU length of stay or postoperative hospital stay. High dose TXA did reduce the volume of perioperative allogenic red blood cell transfused but did not reduce the transfusion of frozen plasma, platelets or cryoprecipitate. There was no statistical difference between treatment arms in incidence of patients requiring re-operation for bleeding.

Critique

The investigators in the OPTIMAL trial have attempted to answer an important clinical question on the optimal dosing of TXA during cardiac surgery requiring cardiopulmonary bypass. The evidence prior to this suggests a significant beneficial haemostatic effect of TXA, yet it had been unknown whether higher doses, delivered by infusion, had a supplementary haemostatic effect, without increasing the potential risks of seizures or adverse thrombotic effects.

Firstly, the investigators must be commended on their robust trial design and conduct of this trial. This was a well-executed, multi-centred, double-blind randomised control trial. The investigators sought to recruit over 3000 patients for this trial, a well thought out sample size based on power calculations generated from using risks margins from previous studies and registry data. This was achieved in a little under two and a half years, even more impressive considering the recruitment period spanned the onset of the COVID-19 pandemic. The study was carried out by four centres within China, and

therefore the application of these results to other ethnic populations should be considered.

Over 13000 patients were screened, and over 10000 patients were excluded. It must be noted that the majority of patients excluded fell outside the target age range of between 18 and 70 years of age. This is noteworthy and may affect external application of these results to the elderly at-risk patient undergoing cardiac surgery, particularly because increased age is thought to be a risk factor associated with TXA-induced seizures.[8] Furthermore, the study included patients undergoing total aortic arch repair; these patients had the highest rate of bleeding in this study and the authors themselves concede the complexity of the surgery may have masked or reduced the dose-dependent effects of TXA.
The study intervention appears to be well thought out, with a rationale behind each of the dosing strategies. Furthermore, every measure had been taken to ensure blinding of the intervention; the same rate of administration was used for each dosing strategy. Outcomes appear to be appropriate to answer the clinical question. The primary efficacy outcome of the proportion of patients requiring red cell transfusion was appropriate in assessing the haemostatic effects of the TXA dosing strategies, particularly given that pre-defined thresholds were used to dictate red cell transfusion. Similarly, the primary safety outcome of all-cause mortality, seizures, thrombotic events and kidney dysfunction had stringent definitions. Perhaps a slight limitation in the trial design was the lack of intraoperative EEG monitoring; diagnosis of seizures was based on clinical signs and therefore their incidence may have been under-reported as they may have presented sub-clinically whilst under anaesthesia.

Overall, this was a thoughtfully designed, well-run trial investigating the effects of high versus low dose TXA infusion in patients undergoing cardiac surgery requiring cardiopulmonary bypass. Their results showed that high dose TXA resulted in fewer patients requiring allogenic blood transfusion and was non-inferior to low dose TXA with respect to complications. While the generalisability and application of the results are slightly limited due to the selective study cohort and lack of ethnic diversity in the study population, the findings of the study undoubtedly add to the existing evidence regarding the use of TXA in cardiac surgery.

Body of Evidence

As the use of aprotinin has gradually been phased out, TXA has been the mainstay anti-fibrinolytic agent that has been used in cardiac anaesthesia to try and mitigate against the risks of peri-operative bleeding. While the haemostatic effects of TXA have been well established historically, the theoretical risk of thrombosis, coupled with potential for inducing seizures, meant its exact indications and applications were unknown. In

2017, the ATACAS investigators conducted a RCT demonstrating that TXA, as compared to placebo, was associated with a lower risk of bleeding without an increased risk of thrombotic complications, albeit with a slightly increased risk of seizures.[3] In this trial, single doses of 50 mg/kg and 100 mg/kg were used, and it was still unknown what the optimal dosing strategy was.

The OPTIMAL investigators have helped to answer this question, demonstrating higher doses, administered by infusion, have additional haemostatic benefit without compromising safety. While the incidence of seizure was still higher in the higher dose cohort (1% vs 0.4%, [Risk difference 0.0%-1.2%, p=0.05]), the incidence was lower than previously published meta-analysis (2.7%) suggesting a protective effect of administration by infusion.[8]

In addition, whilst the OPTIMAL trial pertains to use in patients undergoing cardiac surgery, its findings complement other recent findings in non-cardiac surgical populations. The POISE-3 investigators demonstrated that TXA was associated with lower bleeding complications without an increase in thrombotic risk in patients undergoing non-cardiac surgery.[9] In addition, the WOMAN trial showed in post-partum haemorrhage, TXA use was associated with a mortality benefit, without increasing thrombotic complications.[10] Prior to the publication of OPTIMAL, Taeuber and colleagues demonstrated in a meta-analysis of 216 studies that TXA use was not associated with a risk of thrombotic events irrespective of dosing.[11]

The OPTIMAL trial confirms that TXA, in higher doses, are safe and more efficacious in preventing bleeding in patients undergoing cardiac surgery. Furthermore, its findings support the fact TXA use is not associated with an increase in thrombotic events in heterogeneous patient populations. Prior to OPTIMAL, no randomised control trial existed regarding the dose-dependent effect of TXA infusion on clinical and adverse outcomes. Whilst the dosing regimen employed in OPTIMAL may now become established practice, clinicians must be aware of the external application of their findings and the importance of appropriate patient selection.

Should we be using high dose TXA infusion during cardiac surgery?

We probably should, although more evidence is needed across more ethnically diverse and older patient populations.

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PROTECT

Sessler DI, Pei L, Cui S, Chan MTV, Huang Y, et al. Aggressive intraoperative warming versus routine thermal management during non-cardiac surgery (PROTECT): a multicentre, parallel group, superiority trial. Lancet 2022;399(10337):1799-1808

Introduction

The PROTECT trial aimed to compare clinical outcomes between patients managed with two different temperature targets during major surgery.

Interest in perioperative hypothermia as a modifiable factor in perioperative morbidity has been ongoing for decades. In the absence of preventative measures, convective and radiation heat loss in the absence of effective homeostatic mechanisms due to general or regional anaesthesia leads to almost universal hypothermia, particularly in prolonged surgery. Perioperative hypothermia is associated with post-operative complications including surgical site infections and myocardial ischaemia through impaired immune cell function, peripheral vasoconstriction and decreased skin perfusion, and increased myocardial oxygen demand due to shivering and tachycardia.

Prevention of hypothermia is now an established aspect of perioperative care throughout higher-income countries, and is embedded in clinical practice guidelines, for example, from the National Institute for Health and Care Excellence and the National Royal College of Anaesthetists in the United Kingdom. In the United States, prevention of perioperative hypothermia is listed in the National Hospital Quality Measures Manual,[1] and is cited by the Institute for Health Improvement in the United States as a 'change for improvement'.[2] It is against this backdrop that the authors proposed to study two alternative temperature targets, predominantly in the setting of hospitals in China, where active patient warming was not established practice and thus where clinician equipoise was present.

Synopsis

The PROTECT trial was an investigator-initiated, open-label, multicentre randomised trial comparing an intra-operative temperature target of 37°C with a target of 35.5°C in patients aged 45 years or more with one or more cardiovascular risk factors undergoing major surgery. The trial recruited over nearly 4 years between 2017 and 2021 in 12 centres in China and 1 in the USA, and was reported in The Lancet in May 2022.

Patients were eligible for the trial if they were aged 45 years or more, undergoing surgery expected to last between 2 and 6 hours, expected to need an overnight stay post-operatively, and to have more than half their body surface area available for warming. They were also required to have one or more cardiovascular risk factors (hypertension, previous stroke, known cardiovascular disease, or diabetes). The only exclusions were dialysis dependence and obesity (body mass index > 30 kg/m^2).

Patients in the 'aggressive warming' (intervention) group received pre-warming with a full-body forced air blanket for 30 minutes prior to anaesthesia induction, initially set to 43°C, and intra-operatively were warmed using one or two forced air warmers depending on the surgical site, with a target core temperature of at least 37°C. All intravenous fluids were warmed, and the ambient temperature in the operating room was maintained around 20°C.

Patients in the 'routine thermal management' (usual care) group had no pre-warming. The ambient room temperature in the operating room was maintained around 20°C, and transfused blood was warmed, but intravenous fluids were not routinely warmed. A forced air blanket was applied to either the upper or lower half of the body but was only activated if the core temperature dropped below 35.5°C. Importantly, this was deemed to reflect standard care in China, where over 99% of the study participants were enrolled.
In both groups, core temperature was monitored using an oesophageal or nasopharyngeal temperature probe. Other aspects of care were according to usual clinical practice.

The primary outcome was a composite of myocardial injury after non-cardiac surgery (MINS), non-fatal cardiac arrest, and all-cause mortality within 30 days from surgery. MINS was defined as elevation of troponin above the normal range of presumed ischaemic origin. Secondary outcomes were deep surgical site infection, intra-operative blood transfusion requirement, length of hospital stay, and hospital readmission within 30 days of surgery. Exploratory outcomes included change in haemoglobin concentration, superficial surgical site infection, Quality of Recovery-15 (QoR-15) score at day 3 following surgery, and myocardial infarction within 30 days from surgery (defined as elevated troponin and one other diagnostic feature of ischaemia). All outcome assessments were made by a blinded investigator.

The planned sample size was 5050, based on data from the large Perioperative Ischaemic Evaluation-2 trial3 with a baseline incidence of 10%, 0.1%, and 1% for MINS, non-fatal cardiac arrest, and mortality respectively. This sample size was calculated to provide 90% power to detect a 30% relative risk reduction for the primary outcome at a significance

level of 0.05 after adjustment for interim analyses and an estimated 5% loss to follow-up. Pre-defined subgroup analyses were based on sex, age (<65 or ≥65 years), and type of surgery (orthopaedic, laparoscopic, open abdominal, neurosurgical, urological, or other).

A total of 12,064 patients were screened over nearly 4 years between March 2017 and March 2021, of whom 5,056 were randomized. After withdrawals, 5,013 were included in the primary intention-to-treat analysis. The groups were well-balanced according to baseline characteristics and intra-operative management. Over 50% of the patients underwent laparoscopic procedures, and almost 25% had open abdominal surgery. 97% of procedures were elective, and the mean duration was in excess of 4 hours. Four patients were incorrectly enrolled (all on dialysis, one of the exclusion criteria) but were included in the trial.

There was excellent separation in temperature between the two arms: in the aggressive warming arm, the mean final intra-operative temperature was 37.1°C (standard deviation 0.3) and the mean intra-operative temperature was 36.8°C (standard deviation 0.3). In the routine care arm, the mean final intra-operative temperature was 35.6°C (standard deviation 0.3) and the mean intra-operative temperature was 35.8°C (standard deviation 0.3).

There was no difference in the primary outcome of MINS, non-fatal cardiac arrest, or death within 30 days (246 of 2,497 patients (9.9%) for the intervention group, and 239 of 2,490 patients (9.6%) for the standard care group; relative risk 1.04, 95% CI 0.87 to 1.24). No difference was present between arms for each component of the composite primary outcome considered individually.

No difference was present between treatment groups for any of the secondary outcomes of deep surgical site infection, intra-operative blood transfusion requirement, length of hospital stay, and hospital readmission within 30 days of surgery. Although no statistical tests of significance were undertaken, exploratory outcomes (change in haemoglobin concentration, superficial surgical site infection, QoR-15 score at day 3, and myocardial infarction within 30 days from surgery) were similar between groups.

Pre-specified subgroup analysis (based on age, sex, and type of surgery) revealed no interaction between subgroup and outcome. Per-protocol analysis revealed no difference in the primary outcome from the primary intention-to-treat analysis.

Adverse event rates were reported per group, but no statistical comparisons were performed: 17 serious adverse events occurred in the intervention group versus 30 in

the usual care arm, of which only one was considered possibly related to the study intervention. Non-serious adverse event rates were similar between groups.

Critique

This was a very large and well-conducted trial, which addressed an important clinical question for patients and care providers in the perioperative setting. Partly because the intervention (warming to normothermia) was considered standard of care in higher-income countries, the trial was conducted in a setting where equipoise was still present, with study coordination led from the Cleveland Clinic in the US.

Strengths of the trial included the very large sample size, the multicentre design, the use of blinded outcome ascertainment, a low rate of loss to follow-up, and impressive fidelity with the study intervention, with excellent separation of temperature between groups.
The baseline incidence for each of the components was similar to estimates informing sample size calculation, allowing high levels of confidence in the statistical power of the trial and precision around the estimate of effect.

It could be argued that MINS, although associated with adverse patient-centred outcomes, is not in itself a patient-centred outcome. However, secondary outcomes included length of hospital stay and hospital readmission, which are potentially much more relevant as indicators of recovery from surgery, and none showed any difference between groups.

Of importance is the setting in which the research was carried out and the implications for the external validity of the trial. It is evident that practice in the trial sites differed, at least in some respects, from current practice in higher-income countries, and indeed this was one reason why the study took place in China. There is, however, no prima facie reason why the results of this trial should not be applicable globally. The authors discuss this issue and the justification for the trial in the online appendix, which is a commendable and transparent approach. In particular, the authors highlight the rationale for the choice of target temperatures for the two treatment arms: that core temperature can typically be maintained at or above 35.5°C without the expensive addition of warming blankets and other measures, and for which there was little pre-existing evidence of harmful effects at this temperature, while 37°C represents true normothermia and thus may have been hypothesized to be an optimum target.

The population studied, although intended to be broad, included few patients undergoing orthopaedic or vascular surgery. The latter is a group at high risk of adverse cardiovascular outcomes due to underlying disease and may therefore be the most likely

to benefit from the avoidance of hypothermia. However, all patients had at least one cardiovascular risk factor, so this was a population of patients at least moderate risk of cardiac events.

Overall, the conclusion that warming to 37°C did not result in a decrease in the composite outcome of MINS, non-fatal cardiac arrest, or death within 30 days of major surgery, or any change in secondary outcomes compared with a target temperature of 35.5°C is justified and robust.

Body of Evidence

Prior to the PROTECT trial, practice was informed by a very few small randomized trials, many carried out some years previously, and underpinned by a physiological rationale. Hypothermia is an almost universal feature in patients undergoing anaesthesia in the absence of active preventative measures and stimulates sympathetic nervous system activation and catecholamine release, resulting in vasoconstriction, tachycardia, and increased blood pressure, which increases myocardial oxygen demand and predisposes to myocardial ischaemia.[3,4] If sufficiently severe, hypothermia is uncomfortable and triggers shivering, further increasing oxygen demand.

One single-centre randomized trial, published in 1997, compared active warming to usual care (at that time not involving active temperature management) in 300 patients with known coronary artery disease undergoing major abdominal, vascular, or thoracic surgery. It found a reduced incidence of myocardial ischaemia and post-operative ventricular tachycardia[5] when normothermia was maintained (mean core temperature 36.6°C at the end of surgery) compared with usual care (mean core temperature 35.4°C at the end of surgery). Outcome determination relied principally on Holter monitoring, leading to an incidence of myocardial ischaemia of around 1%, whereas with the advent of high sensitivity Troponin testing, it is now considered to be greater than 10%.[6] Furthermore, the incidence of ventricular tachycardia was remarkably high, at 7.9% in the hypothermic group. In short, perioperative practice in 1997, and the corresponding risks and benefits, may be quite different today.

One other small randomized trial, involving 100 patients undergoing open abdominal aneurysm surgery, found no improvement in patient outcomes with normothermia (36.3°C) compared with hypothermia (35.6°C).

In addition to cardiac outcomes, hypothermia has previously been shown to be associated with wound infections, thought to be mediated by vasoconstriction, decreased oxygenation, and impaired immune function. In one small randomized trial including 200 patients undergoing colorectal resection, normothermia (mean core

temperature 36.6 ± 0.5°C at the end of surgery) resulted in a decreased incidence of surgical wound infection compared with hypothermia (mean core temperature 34.7 ± 0.6 °C at the end of surgery), as well as reduced length of hospital stay.[7]

Based on these small trials, active warming of patients undergoing surgery to normothermia or near normothermia became established practice in many countries and an integral part of perioperative guidelines.[2,8] Vast effort and expense have been utilized in the pursuit of intraoperative normothermia, involving pre- and intraoperative forced air warming, surface warming, intravenous fluid warmers, and other methods.

The PROTECT trial aimed to address an important question for patients and clinicians but, from a higher-income country perspective, was investigating the de-adoption of an established practice, with all the challenges of equipoise that this entails. The authors, therefore, undertook the trial in a healthcare setting in which perioperative warming had never been consistently adopted. The PROTECT trial is a very large and robust randomized trial that dwarfs all the pre-existing evidence on the topic.

Reasons why the PROTECT trial results were incongruous with previous trials may be related to the significant passage of time since previous trials, which were carried out in the mid-1990s.[5,7] Anaesthesia practice has moved on in the last 25 years, and it may be that the impact of hypothermia on outcomes is correspondingly lower than it once was. Alternatively, it may be that the PROTECT trial overcame biases that were present in earlier studies.

In summary, a permissive strategy, allowing the temperature to fall close to 35.5°C before initiating active warming measures, was safe and could be adopted as routine without compromising patient safety.

Should we use a temperature target of 35.5 intra-operatively?

Yes, this was safe and well-tolerated. A permissive target for maintenance of core temperature can be adopted as routine without compromising patient safety.

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ALBICS

Pesonen E, Vlasov H, Suojaranta R, Hiippala S, Schramko A; Wilkman E, et al. Effect of 4% Albumin Solution vs Ringer Acetate on Major Adverse Events in Patients Undergoing Cardiac Surgery With Cardiopulmonary BypassA Randomized Clinical Trial. JAMA 2022;328(3):251-258

Introduction

Since the first successful application of cardiopulmonary bypass (CPB) in 1953, CPB has become the standard of care for many cardiac procedures.[1] CPB provides optimal operating conditions for the surgeon by ensuring a bloodless, immobile operating field while delivering oxygenated blood to the body.[2] Despite the clear advantages of CPB inherent risks related to direct contact of blood with the artificial extracorporeal circuit include activation of the coagulation and the immune systems which may result in a state of systemic inflammation and multi-organ failure.[3] Moreover, the presence of air within the bypass circuit can lead to an air embolism or air lock if it is present on the arterial or venous side of the circuit respectively.[2] To prevent this the CPB circuit is deaired with fluid, a process known as priming.

In CPB surgery peri-operative fluid management is essential to maintain an effective circulatory volume to allow adequate tissue oxygen delivery. CPB can result in intravascular depletion due to polyuria, capillary leakage, and fluid redistribution.[4] Moreover, the associated inflammatory insult may lead to profound vasoplegia.[4]
There is a wide variation in practice regarding fluid management in cardiac surgery. A European survey conducted in cardiac centres in 18 different countries highlighted this variation and revealed that 51.5% of respondents used balanced crystalloids for CPB priming with a further 31.1% using a combination of crystalloid and synthetic colloid fluid therapy.[5]

There is a lack of robust evidence to guide clinicians on which type of fluid to use and, as such, clinical equipoise has developed surrounding the use of albumin or balanced crystalloids. The ALBICS trial provides robust evidence regarding the use of 4% albumin compared with Ringer acetate solution in patients undergoing on-pump cardiac surgery.

Synopsis

Pesonen et al., conducted a randomized, double-blind, single-center clinical trial at Helsinki University Hospital, Helsinki, Finland. The aim of the trial was to compare the

safety and effectiveness of 4% albumin solution versus Ringer acetate solution as the priming and perioperative intravenous volume replacement strategy in patients undergoing cardiac surgery with cardiopulmonary bypass. ALBICS was published in the Journal of the American Medical Association on 19th July 2022.

Between March 2017 and January 2020 participants were randomised in a 1:1 ratio, using an electronic platform, to receive either 4% albumin solution (n = 693) or Ringer acetate solution (n = 693). The composite end point of MAEs comprised of ≥1 of the following: death, myocardial injury, acute heart failure, re-sternotomy, stroke, arrhythmia, bleeding, infection, or acute kidney injury (AKI).

Eligible patients included those aged 18-90 years old who were undergoing the following primary or repeat open heart surgery procedures independently or in combination: coronary artery bypass graft surgery; aortic, mitral, or tricuspid valve replacement or repair; aortic root or ascending aortic surgery without hypothermic circulatory arrest; or the maze procedure. Patients were excluded if they were scheduled for immediate emergency surgery or correction of a congenital cardiac defect. Patients were also excluded if infection was expected to compromise postoperative recovery or if they had ongoing heart failure or end- stage kidney disease. Finally, those with either an acquired (including drug induced) or congenital tendency towards haemorrhage were excluded.

The trial intervention consisted of two phases. The first phase involved the use of 4% albumin as the priming fluid for CPB. The second phase involved the use of 4% albumin as the fluid therapy of choice for intravenous volume expansion during the operation and for the first 24 hours in the intensive care unit (ICU) or until discharged from the ICU (whichever occurred first). Dosing of the study fluid was based on clinical decision. Robust steps were taken to ensure that the trial patients and the entire study group, including study nurses and personnel taking care of the patients, were blinded to randomisation. This involved the use of opaque cover bags and coloured infusion tubes. In the control group Ringer acetate solution was used to prime the CPB circuit and for perioperative volume expansion.

The primary outcome was the number of patients with at least 1 MAE during the study period of 90 days. A previous cohort study at Helsinki University Hospital estimated the incidence of MAEs to be 30%.[6] Thus, it was calculated that a sample size of 1242 patients would provide 80% power to detect an absolute difference of 7.5% in the primary outcome between the treatment arms with a 2-sided P value of 0.05. However, in an analysis among the first 550 patients it was determined that the incidence of the primary end point was 42%. Therefore, to retain the detection of the absolute

difference of 7.5% between the groups an independent statistician increased the sample size to 1386 patients.
Secondary outcome measures included the total number of MAEs; incidence of major adverse cardiac event (cardiac death, myocardial injury, acute heart failure, arrhythmia); amount of blood products transfused; total fluid balance; total measured blood loss; AKI development; days alive without mechanical ventilation during 90-day follow-up; days alive outside ICU during 90-day follow- up; days alive at home during 90-day follow-up; and 90-day mortality.

Subgroup analyses were performed according to preoperative GFR, EuroSCORE II and presence or absence of aortic stenosis. Safety analysis was performed based on comparison of serious adverse events (SAEs) between the study groups. Statistical analysis was conducted in accordance with a pre-defined analysis plan with the exception of the post hoc analyses. Participants were analysed according to their randomisation group.

For the primary end point there were no missing end point data. The primary outcome was compared between the study groups using the Fisher exact test and a binomial regression model was used to estimate both relative risk and absolute differences. The secondary outcome, subgroup, and safety analyses were conducted with a 2-sided significance level of 0.05 without pre-defined calculations of statistical power.

3627 patients were screened between March 2017 and January 2020. 1084 patients were excluded for procedure related reasons and 624 patients were excluded for patient related reasons. 1407 patients were recruited and randomised. 21 patients were withdrawn prior to the onset of CPB due to changes in the operative management plan. Ultimately, in each arm of the trial 693 patients were included in the primary analysis.

Baseline patient characteristics, laboratory values, and surgical procedure type were reasonably well balanced between groups. The mean age in both groups was 65 with a similar proportion of males and females in each group (albumin group 79% male, Ringer group 78% male). Pre-operative laboratory values were similar between groups with a mean GFR of 80, haemoglobin of 14.1 and platelet count of 230. The median EuroSCORE II in each group was 1.7. The most common indication for on pump cardiac surgery was coronary artery bypass grafting (CABG). The number of participants undergoing 2 or more procedures was similar between groups (albumin group 130 patients; Ringer group 131 patients). The mean duration of CPB was similar between groups (albumin group 109 minutes; Ringer group 110 minutes) and the mean aortic cross clamp time was similar (albumin group 81 minutes; Ringer group 82 minutes). Patients in the albumin

group received a median of 2150 mL (IQR, 1598-2700 mL) of fluid whereas those in the Ringer group received 3298 mL (IQR, 2669-3500 mL).

The study investigators determined there was no statistically significant difference in the 90-day incidence of MAEs between the Albumin 4% and the Ringer acetate fluid groups (37.1% vs 33.8%; P = 0.22). Exploratory analyses of individual components of the composite primary outcome revealed a significantly lower incidence of myocardial injury in the albumin group (RR 0.44; 95% CI 0.28 to 0.68; P < 0.001). However, the incidence of bleeding (RR 1.73; 95% CI 1.12 to 2.68; P = 0.01), resternotomy (RR 1.85; 95% CI 1.28 to 2.68; P = 0.001), and infection (RR 1.45; 95% CI 1.07 to 1.97; P = 0.02) were significantly higher in the albumin group. No statistically significant differences existed in the other components of the primary outcome.

The total fluid balance during the intervention period was significantly lower in the albumin group (−1277 mL; 95% CI −1433 to −1120 mL; P < 0.001). However, blood loss via chest tube drainage was higher in the albumin group (178 mL; 95% CI 138 to 219 mL; P < 0.001). This was supported by secondary outcome analyses which revealed higher red blood cell (difference, 107 mL; 95% CI 60 to 155 mL; P < .001) and platelet transfusion (difference, 71 mL; 95% CI 41 to 100 mL; P < 0.001) requirements in the albumin group. There were no other statistically significant differences in the remaining secondary outcomes.

The incidence of infection in patients with aortic stenosis was proportionally significantly greater in the albumin group (Estimation of interaction 2.35; 95% CI 1.03-5.32; P = 0.04). Moreover, fluid balance in patients with a high EuroSCORE II was proportionally significantly greater in the albumin group (Estimation of interaction -364; 95% CI -671 to -58; P =0.02). No other differences existed in the pre-defined subgroups. A post hoc analysis revealed that increased bleeding was significantly associated with both resternotomy (RR, 11.16; 95% CI 7.57 to 16.45; P <0 .001) and infection (RR, 3.16; 95% CI 2.01 to 4.97; P <0 .001).

At least 1 SAE occurred in 103 of 693 patients (14.9%) in the Ringer group and in 114 of 693 patients (16.5%) in the albumin group (RR, 1.11; 95% CI 0.87-1.41; P = 0.46). The authors reported no significant difference in the total number of SAEs with a total of 283 (40.8%) in the Ringer group and 312 (45%) in the albumin group (RR, 1.10; 95% CI 0.98 to 1.25; P = 0.13). The most common SAEs were the development of pulmonary emboli (11 [1.6%] in the albumin group and 8 [1.2%] in the Ringer group) and post pericardiotomy syndrome (9 [1.3%] in both groups).

Critique

ALBICS is the first large interventional trial to clearly demonstrate a lack of greater benefit of albumin therapy compared with balanced crystalloid therapy in cardiac surgery in terms of effectiveness and safety. The trial design is robust with the trial protocol and statistical analysis plan published prior to completion of data collection.[7] This was a well conducted trial, with an impressive effort to ensure double blinding.

The composite endpoint of MAE contains individual components encompassing a range of significant clinical end points which have important health and economic implications. Several important aspects of the ALBICS trial limit the interpretation of the trial outcomes and restrict the external validity of the study. Firstly, the single centre nature of this study limits the extrapolation of these results to other cardiac centres. Secondly, a survey of European cardiac surgical centers identified that gelatin was the colloid of choice for CPB priming. Similarly, if colloids were used for intra-operative fluid management, gelatin was a more popular choice than albumin.[5] Similarly, in a survey performed in cardiac centres in the USA it was revealed that albumin 5% was the most commonly used colloid in the peri-operative setting.[8] Moreover, this survey identified that approximately one third of perfusionists utilised a mixture of crystalloids and albumin to prime the CPB circuit. Therefore, it is difficult to extrapolate the results of the 4% albumin used in this study to the likes of gelatin, hydroxyethyl starch solutions, and other tonicities of albumin. In addition, any attempt to extrapolate the ALBICS outcomes to scenarios which employ a combination of crystalloid therapy and colloid therapy should be done with extreme caution.

Of note, the exclusion criteria exclude an important cohort of unwell and unstable patients as highlighted by the median EuroSCORE II of 1.7 in both the albumin and Ringer acetate group. This limits the generalizability of findings to a key subgroup who may potentially benefit from albumin therapy. It has previously been demonstrated by Rex and colleagues that colloid priming of CPB was associated with significantly less fluid extravasation and reduced intraoperative fluid replacement requirements which may be particularly relevant in an unstable population, such as patients with low left ventricular ejection fractions or those with end-stage renal disease.[9]

Finally, the primary composite endpoint contains outcomes such as arrythmia for which there is limited biological plausibility of albumin having an effect. Unfortunately, the study was not powered to determine the effect of albumin on other individual primary outcome components for which there is a more robust rationale for investigation.

The ALBICS trial has determined that the use of 4% albumin solution for CPB prime and perioperative volume replacement in elective low-risk cardiac surgery, compared with

Ringer acetate solution does result in improved clinical effectiveness or safety outcomes. Moreover, analysis of individual components of the primary composite outcome and secondary outcomes suggests a potential for harm in using albumin due to an association with increased bleeding, transfusion requirements, infection and need for re-operation.

Body of Evidence

ALBICS addresses an important clinical question regarding the role of albumin in cardiac surgery. Albumin has become a popular fluid choice in cardiac surgery as a result of evidence arising from pre-clinical and small clinical trials.

The putative protective effects of albumin, such as its anti-inflammatory, antioxidant, and endothelial barrier stabilising properties, are well documented.[10,11] Moreover, early work in cardiac surgery demonstrated that hydroxyethyl starch solutions and gelatin were associated with impaired haemostasis whereas albumin had minimal effect on thromboelastometry derived variables.[12,13] However, a retrospective, Australian single-center cohort study[14] by Matebele and colleagues compared outcomes in 1264 patients who received 4% albumin and 1330 patients who did not. Those who received albumin therapy were more likely to require reoperation for bleeding and/or tamponade (6.1% vs 2.1%; OR, 2.84; 95% CI 1.81–4.45; $p < 0.01$) and to receive packed red cell transfusions ($p < 0.001$). This is consistent with the increased bleeding, reoperation, and transfusion requirements observed in the albumin arm of the ALBICS trial.

Albumin usage may also have been driven by evidence which identified hypoalbuminaemia as an independent risk factor for poor patient outcomes. de la Cruz et al[15] identified that a preoperative albumin level less than 35 g/L was associated with a significantly lower long term survival rate in CABG patients (65% +/- 7% versus 86% +/- 3%; hazard ratio 2.2; 95% CI: 1.4 to 3.6; P=0.001) than patients without hypoalbuminemia. Similarly, Berbel-Franco and colleagues[16] demonstrated that patients with low postoperative albumin levels also had reduced long term survival (5-year mortality: 94.3% normal subgroup (≥35 g/L), 87.4% low albumin deficit (30–34.9 g/L), 83.1% moderate albumin deficit (25–29.9 g/L) and 72.4% severe albumin deficit (< 25 g/L); $P < 0.001$).

The use of albumin in cardiac surgery has been extrapolated from RCT data involving other cohorts of critically ill patients. This relates to the unique host response elicited by exposure to CPB which shares many of the characteristics of major trauma and sepsis.[17]

The SAFE trial was a multicenter, randomized, double-blind trial which compared the effect of fluid resuscitation with 4% albumin or 0.9% saline on mortality in patients admitted to ICU. 3497 patients were assigned to receive albumin and 3500 to receive 0.9% saline. The SAFE trial failed to demonstrate a survival benefit in those receiving

albumin with 726 deaths in the albumin group, as compared with 729 deaths in the saline group (relative risk of death, 0.99; 95% CI 0.91 to 1.09; P = 0.87). However, in a subgroup of patients with sepsis there was a potential signal of efficacy in those receiving albumin (RR, 0.87; 95% CI 0.74 to 1.02; P=0.09).[18]

The subsequent ALBIOS trial directly investigated this patient cohort.[19] ALBIOS was a large Italian multicenter, open label trial, in which patients with severe sepsis were randomised to receive either 20% albumin and crystalloid solution or crystalloid solution alone. In the albumin group, the target serum albumin concentration was 30 g/L. 1810 patients were randomised and analysed, 903 in the albumin group and 907 in the control group. During the first 7 days, patients in the albumin group had a higher mean arterial pressure (P=0.03) and lower net fluid balance (P<0.001). However, there was no difference in the primary outcome of 28-day mortality; albumin group (31.8%) versus control (32.0%) (RR, 1.00; 95% CI 0.87 to 1.14; P = 0.94). A post hoc subgroup analysis which included 1121 patients with septic shock demonstrated a significantly reduced mortality at 90 days in the albumin group (RR 0.87; 95% CI, 0.77 to 0.99).

The FRISC trial was a single centre open label study which randomised patients with cirrhosis and infection induced hypotension to receive either 5% albumin (154 patients) or 0.9% saline (154 patient).[20] The primary outcome was the reversal of hypotension at 3 hours which was more likely in the albumin group, 11% vs 3.2% (OR, 3.9; 95% CI 1.42 to 10.9; P=0.008) and mortality was also lower in the albumin group at 1 week (43.5% vs 38.3%; P=0.03).

The clinical evidence regarding the use of albumin in the cardiac surgery patient population is sparse. A retrospective cohort study in the USA analysed 1,095 patients who received 5% albumin with crystalloid solutions and 1,095 patients who received crystalloids alone on the day of or the day following on-pump cardiac surgery for valve and/or coronary artery procedures.[21] Patients were selected by propensity score matching. In the propensity-score matched cohort, receipt of perioperative 5% albumin was associated with a decreased risk of in-hospital mortality (OR 0.5; 95% CI 0.3 to 0.9; P = 0.02) and lower all-cause 30-day readmission rates (OR 0.7; 98.3% CI 0.5 to 0.9; P < 0.01).

The results from the ALBICS trial suggest that routine use of albumin should be avoided for elective low-risk patients undergoing cardiac surgery with CPB. However, ongoing work is likely to focus on identifying the role of albumin in specific subpopulations and to establish if there is an indication for combined albumin and crystalloid therapy. The ongoing ALBumin Infusion and acute kidney injury following Cardiac Surgery trial is an

open-label, multicentre, randomised controlled trial evaluating the impact of postoperative 20% albumin infusion on kidney function after high-risk cardiac surgery.[22]

Should we use 4% Albumin in patients undergoing on pump cardiac surgery?

The results of the ALBICS trial do not support the use of 4% albumin solution as a priming and perioperative intravenous volume replacement solution in elective low-risk patients undergoing on pump cardiac surgery.

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POISE 3

Devereaux PJ, Marcucci M, Painter TW, Conen D, Lomivorotov V, Sessler DI, et al. Tranexamic Acid in Patients Undergoing Noncardiac Surgery. N Engl J Med 2022;386(21):1986–97

Introduction

Perioperative bleeding is widely acknowledged as the most common complication linked to all forms of surgery, and it is independently correlated with morbidity and mortality.[1,2] It is particularly evident in non-cardiac surgeries where major bleeding has been found to be the highest correlating factor with 30-day mortality.[3] Given the invasive nature of surgeries, a certain degree of perioperative blood loss is to be expected. However, this loss can be significantly exacerbated due to factors such as vascular injury, inherent bleeding disorders, or acquired coagulation disorders resulting from haemodilution, clotting factor deficiency, or consumption. The use of prophylactic and therapeutic strategies to prevent large-volume perioperative blood loss in surgical populations may mitigate the associated negative outcomes.

Currently, there are only a few pharmacotherapies that can either prevent or treat perioperative bleeding apart from medications used to reverse anticoagulants or optimise coagulation pathways. The most widely known among these is tranexamic acid (TXA). TXA is a synthetic lysine analogue that binds to plasminogen and prevents it from binding to fibrin, thereby inhibiting fibrinolysis.[4] Its usage is prevalent in cardiac surgery as strong evidence shows that TXA reduces the risk of major bleeding compared to placebo, without a corresponding increase in thrombotic events.[5] Similarly, the benefits of TXA are observed in the obstetric population undergoing caesarean sections, and in patients who undergo lower limb arthroplasty.[6,7]

However, it remains unclear whether the widespread use of TXA in patients undergoing non-cardiac, non-orthopaedic surgery is beneficial. This formed the basis for the Perioperative Ischaemic Evaluation-3 (POISE-3) trial, which aimed to investigate if the use of TXA resulted in a lower incidence of major bleeding, without leading to an increase in adverse cardiovascular events.[8]

Synopsis

The aim of this trial was to evaluate whether tranexamic acid (TXA) resulted in a lower incidence of major bleeding in patients undergoing non-cardiac surgery who were at risk for bleeding and cardiovascular events. It also aimed to assess whether TXA was non-inferior to placebo in causing an increase in adverse cardiovascular events.
The Perioperative Ischaemic Evaluation 3 (POISE-3) was a large, international, randomised controlled trial that enrolled patients from 22 countries. Participants were randomised to receive either TXA or a placebo. Additionally, a partial factorial design was employed for patients receiving one or more antihypertensive medications to investigate the effects of either a peri-operative hypotension-avoidance strategy or hypertension-avoidance strategy on the outcomes.

Participants eligible for the study were 45 years or older, were undergoing inpatient non-cardiac surgery, and had one or more risk factors for bleeding and cardiovascular complications. These risk factors included known atherosclerotic disease, undergoing major surgery, being 70 years of age or older, and having a serum creatinine level of more than 175 µmol/L (2.0 mg/dL). Key exclusion criteria encompassed undergoing cardiac or intracranial surgery, planned use of TXA, a low-risk surgical procedure based on clinical judgement, and a creatinine clearance below 30 ml/min or receiving long term dialysis.

Eligible patients were randomised using a central computerised system with the use of block randomisation, stratified according to the centre. Patients were assigned in a 1:1 ratio to receive TXA (1-g intravenous bolus) or a placebo at the start and end of surgery. Additionally, patients were randomised, also in a 1:1 ratio using a partial factorial design, to a hypotension-avoidance strategy or a hypertension-avoidance strategy. The research team followed up with patients during their hospital admission and contacted them on day 30 for further follow-up.

The primary efficacy outcome was a composite bleeding outcome, defined as life-threatening bleeding, major bleeding, or bleeding into a critical organ by Day 30 post-randomisation. The primary safety outcome was a composite cardiovascular outcome, defined as myocardial injury following non-cardiac surgery, non-haemorrhagic stroke, peripheral arterial thrombosis, or symptomatic proximal venous thromboembolism. Secondary and tertiary outcomes included individual components of the composite efficacy and safety outcomes, a net risk/benefit outcome, transfusion of at least one unit of packed cells, amputation, and seizures.

To affirm the primary safety non-inferior hypothesis that TXA was non-inferior to placebo with respect to the composite cardiovascular outcomes, the upper boundary for

the one-sided 97.5% confidence interval for the hazard ratio (HR) had to be below 1.125, and the one-sided p value had to be less than 0.025. The goal was to recruit 10,000 patients, which would demonstrate this with 95% power assuming a placebo event rate of 11%, and an actual HR of 0.9. Additionally, this sample size would also provide over 90% power to detect a HR less than 0.75 for the primary efficacy outcome, assuming a placebo event rate of 7%.

In total, 9,535 patients were recruited for the trial. This trial only discussed the results of the use of TXA; the results of the blood pressure management randomisation will be published subsequently. The slight shortfall from the planned 10,000 was due to a financial deficit arising from the Covid-19 pandemic. At the time of discontinuation of recruitment, the steering committee was unaware of the results but was aware of a higher than predicted incidence of both composite efficacy and safety outcomes. This sample size was sufficient to allow a 90% power for the efficacy outcome, and 98% for a non-inferiority margin for the safety outcome.

The groups were balanced at baseline, and 30-day follow-up data was completed for 99.9% of recruited patients. The average patient age was 69.4 years, and women made up 43.9% of the cohort. The majority of the procedures were non-orthopaedic, non-cardiac surgeries (76.8%), and 96.3% of the patients received both doses of the trial agent.

The composite bleeding outcome event occurred in 9.1% of the TXA group and 11.7% of the placebo group (HR 0.76; 95% CI 0.67 to 0.87, two-sided p<0.001 for superiority). The composite cardiovascular outcome occurred in 14.2% of the TXA group and 13.9% in the placebo group (HR 1.02, 95% CI 0.92-1.14, one-sided p=0.04 for non-inferiority). Secondary outcomes showed treatment with TXA was associated with significantly less major bleeding (HR 0.72 (0.63-0.83)) but not life-threatening bleeding (HR 0.99 (0.76-1.36)). The incidence of bleeding independently associated with death after surgery was significantly less in the TXA group (HR 0.76 (0.67-0.87)).

Critique

The Poise-3 investigators have undertaken the task of answering an essential clinical question about the use of TXA in patients undergoing non-cardiac surgery who are at risk of bleeding. Although there have been benefits linked with its use in other surgical populations, no sufficiently large trial has been able to offer a robust recommendation on its routine use in patients undergoing non-cardiac surgery. It is admirable that Devereaux and colleagues managed to conduct such an extensive, multi-centred, international randomised control trial within this timescale, particularly considering that their recruitment period spanned the Covid-19 pandemic. The design and execution of

the trial have undoubtedly benefited from the considerable experience gleaned by the trialists from their two previous large-scale perioperative trials, Poise-1[9] (Perioperative use of Beta-blockers) and Poise-2[10] (Perioperative use of Aspirin).

There is no doubt that the trial has a well-thought-out, robust design. The 2x2 factorial design allows further exploration of peri-operative blood pressure management strategies (not discussed here) and did not lead to imbalances at baseline. In addition, the targeted and achieved calculated sample size allowed for sufficient statistical power from which conclusions could be drawn. Although recruitment had to be stopped early, the authors demonstrated that the study was 90% powered to determine efficacy. The primary efficacy outcome was a composite outcome based on bleeding, and while these are traditionally interpreted with caution, it seems appropriate considering the heterogeneity that exists in the definition of major haemorrhage in the literature.

The non-inferior margin of the composite primary safety outcome is worth discussing. It was determined that for non-inferiority the upper limit of the confidence interval had to be below a hazard margin of 1.125, corresponding to a relative risk increase of 12.5%. This figure was based on the POISE-2 trial, where 12.5% was half the relative risk used to show the superiority of aspirin to placebo. As a result, the non-inferior margin for POISE-3 was not met despite having an almost identical incidence of the cardiovascular safety outcome. There may be an argument that the 12.5% non-inferiority margin was too stringent, and a lower margin might have been more pragmatic.

The trial aimed to include patients at risk of both cardiovascular and bleeding complications. Initially, it was estimated that the primary safety outcome would occur in 11% of the placebo group. However, the final results showed the incidence was closer to 14%. While this might be explained by the inclusion of such high-risk individuals, it must be taken into consideration that only around 64% of both treatment and control cohort received pharmacological thromboprophylaxis post-operatively.

An important exclusion criterion for this trial was anyone with a previous seizure disorder. TXA has had a long history of association with seizures, most recently, a meta-analysis demonstrated doses over 2g were associated with an increased incidence of seizures.[11] Interestingly, though the numbers are small, 10 patients in the TXA group versus 3 patients in the control group suffered from a seizure, indicating that the risk isn't entirely negated.

In summary, the POISE-3 trial showed that in patients at risk of bleeding and cardiovascular complications of surgery, TXA was superior to placebo in preventing bleeding but did not demonstrate non-inferiority to placebo in the composite

cardiovascular safety outcome. This was a well-executed trial, without any fundamental methodological flaws. Interpretation of the results should be contextualised to individual patients in the clinical environment, understanding that the incidence of the primary cardiovascular outcome was similar in both groups and the lack of non-inferiority shown may have been due to a too stringent non-inferiority margin.

Body of Evidence

The usage of TXA and its precise indications have been widely discussed in the literature. It's now clear from an abundance of evidence that TXA accelerates haemostasis and ultimately reduces death secondary to bleeding. CRASH-2,[12] one of the seminal papers on its use in trauma, showed that a 1g bolus and a 1g infusion over 8 hours resulted in an absolute risk reduction of 1.5% in all-cause mortality. Following this, CRASH-3[13] demonstrated that in patients presenting with probable traumatic brain injury, its administration was associated with a reduction in head injury-related death if treated within the first three hours. The use of TXA has also been well documented in the obstetric population; the WOMAN trial[14] showed that in patients suffering a post-partum haemorrhage, the administration of TXA was associated with a 0.4% absolute risk reduction in mortality due to bleeding, with no increase in adverse effects.

TXA also has its uses in prophylactically reducing the risk of bleeding. In orthopaedic surgery, TXA use has been shown to significantly reduce blood transfusion in those undergoing lower limb total joint arthroplasty.[7] Additionally, its use has been well established in cardiac surgery; the ATACAS trial[5] showed TXA at induction resulted in an absolute risk reduction of 1.4% in bleeding, without a higher risk of death or thrombotic complications. POISE-3 fills the knowledge gap regarding the use of TXA in the non-cardiac surgical population.

While non-inferiority was not shown, it is important to integrate these findings with recent meta-analyses. In 2021, Taeuber and colleagues, in a meta-analysis and meta-regression of 216 studies and 125,550 patients, demonstrated there was no increased risk of thromboembolic events with the use of TXA.[15] Similarly, Murao et al demonstrated similar findings in a meta-analysis of over 100,000 patients with no increase in thrombotic events.[11] Ultimately, POISE-3 supports the use of TXA in patients undergoing non-cardiac surgery who are at high risk of bleeding. Their findings, along with the bulk of the literature, would suggest that there is likely no additional risk of deleterious thrombotic complications occurring.

Should we be using TXA for noncardiac surgery in patients at high risk of bleeding and cardiovascular complications?

Yes, when we consider all the evidence, TXA can prevent bleeding complications without increasing adverse cardiovascular events.

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Rehabilitation Trials

TEAM

Hodgson CL, Bailey M, Bellomo R, Brickell K, Broadley T, Buhr H, et al. Early Active Mobilization during Mechanical Ventilation in the ICU. N Engl J Med 2022;387(19):1747-1758

Introduction

Across the globe, an estimated 13 to 20 million people receive treatment in intensive care units (ICUs) every year.[1] A significant majority of these patients, around 70 to 80 percent, manage to survive their intensive care stay. However, upon recovery, they are often found to be burdened by a range of sequelae. One of the most common and challenging problems they face is generalised weakness, a condition that can be attributed to ICU-acquired weakness (ICUAW) syndromes. The incidence of these syndromes is about 40 percent, though this figure varies depending on the method of diagnosis—clinical diagnosis records an incidence of 32 percent, while electrophysiological diagnosis shows a higher rate of 47 percent.[2]

ICUAW notably affects patients who have undergone mechanical ventilation for periods extending beyond 48 hours. This condition results in a rapid wasting of skeletal muscles and forms part of the pathophysiology of critical illnesses, with several factors contributing to its development.[3]

The impact of ICUAW is substantial, affecting a considerable segment of ICU patients. It carries serious consequences, leading to extended hospital stays, hindered recovery, and delays in weaning patients off mechanical ventilation.[4,5] Moreover, it increases the risk of death. The problem is significant enough to warrant urgent attention and intervention.
Several solutions have been proposed to combat this problem, but they all come with their own set of challenges. One such proposition is the early mobilisation of ICU patients. This method has the potential to reduce the length of hospital stays and improve patients' functional status upon discharge. Despite its potential benefits, incorporating it into routine clinical practice presents several hurdles. Barriers can be patient-related, structural, related to the ICU culture, or process-related.[6] The PADIS guidelines do recommend mobilisation, but they fail to provide specific guidance on the timing or the regimen to be followed.

To address these challenges, the TEAM clinical trial is currently underway. This study tests the hypothesis that early active mobilisation may increase the number of days that

patients are alive and out of the hospital by day 180. This is compared to the standard level of mobilisation in the ICU for adults who are undergoing mechanical ventilation. Through this trial, the medical community hopes to find a more effective way to combat the debilitating effects of ICU-acquired weakness.

Synopsis

The aim of this international, multi-centre, randomised, controlled trial was to evaluate the effects of early mobilisation, which includes sedation minimisation and daily physiotherapy, compared to the usual care provided in each ICU, on the number of days that adult patients in the ICU undergoing mechanical ventilation were alive and out of the hospital by day 180. The study aimed to address the significant problem of ICU-acquired weakness, which affects a large portion of ICU patients and has serious consequences on their recovery and overall health.

The trial received funding from the National Health and Medical Research Council of Australia and the Health Research Council of New Zealand. It was endorsed by the Australian and New Zealand Intensive Care Society and the Irish Critical Care Trials Group.

The criteria for eligibility in this trial were adults aged 18 years or older who were expected to undergo mechanical ventilation in the ICU beyond the calendar day after randomisation. It was also required that these patients' conditions were sufficiently stable to make mobilisation potentially possible. The stability of the patients was gauged based on the absence of certain cardiovascular and respiratory conditions. Exclusions were made for those with dependency in any activity of daily living in the month before hospitalisation, rest-in-bed orders, and proven or suspected acute primary brain or spinal injury. Furthermore, the trial defined subgroups based on baseline characteristics such as pre-hospitalisation disability level, age, illness severity, diagnosis, and frailty.

Random assignment of patients was conducted using a 1:1 ratio to receive either early mobilisation or usual care, through a centralised web-based interface. The assignment sequence was generated by the trial statistician using computer-generated random numbers, stratified according to the trial centre with variable block sizes.

In the early-mobilisation group, experienced physiotherapists led the intervention, partaking in interdisciplinary discussions and reviews of a safety checklist. The intervention was hierarchical and started after randomisation with daily physiotherapy, which was individually tailored to achieve the highest possible level of mobilisation deemed safe for each patient at the initiation of daily therapy. The highest level of

mobilisation was provided for as long as possible before a step-down to lower levels of activity if the patient became fatigued, as measured by the ICU Mobility Scale. Those in the usual-care group received a level of mobilisation that was typically provided at each site. Concomitant care for both groups was guided by treating clinicians. Patients received the trial treatment while they were in the ICU for up to 28 days after randomisation. Given the nature of the intervention, blinding of mobilisation in the ICU was not possible. However, trained staff who were unaware of trial-group assignments ascertained patient-reported outcomes, and the statistical analysis was performed in a blinded manner.

The primary outcome of the study was the number of days that patients were alive and out of the hospital at day 180. Secondary outcomes included mortality at 180 days, the number of ventilator-free days and days out of the ICU from randomisation to day 28, and patient-reported outcome measures such as quality of life and function in survivors at day 180. Prespecified serious adverse events were also monitored throughout the trial.

Based on the standard deviation of the primary outcome in the pilot study, it was calculated that enrolling 750 patients would provide 90% power to detect a 7-day between-group difference with a two-sided alpha of 0.05, after allowing for 15% inflation to account for a nonparametric distribution and 5% loss to follow-up. The analysis of the primary outcome was performed in the intention-to-treat population, which included all enrolled patients except those who had withdrawn consent for data use.

Between February, 2018, and November, 2021, 750 patients from 49 hospitals across six countries were randomised into an early-mobilisation group (372 patients) and a usual-care group (378 patients). After some withdrawals and losses to follow-up, data was available for 99.6% of the patients. Both groups were similar at the start of the trial.

The trial focused on early mobilisation in the Intensive Care Unit (ICU). Active exercise, standing, and walking were considered mobilisation milestones. The mean daily duration of active mobilisation was 20.8 ± 14.6 minutes in the early-mobilisation group and 8.8 ± 9.0 minutes in the usual-care group. This means the early-mobilisation group received, on average, about 12 more minutes of mobilization per day (95% CI, 10.4 to 13.6) The most common barriers to mobilisation in the early-mobilisation group were sedation, agitation, and physiological instability, which were in line with the trial protocol.

The primary outcome measured was the number of days that the patients were alive and out of the hospital at 180 days after randomization. The median number of days alive

and out of the hospital was 143 days (interquartile range, 21 to 161) in the early-mobilization group and 145 days (interquartile range, 51 to 164) in the usual-care group. The absolute difference was -2.0 days, with a 95% confidence interval of -10 to 6 days and a p-value of 0.62, indicating no significant difference between the two groups for this outcome.
An important secondary outcome was mortality by day 180, which occurred in 22.5% of patients in the early-mobilization group and in 19.5% of those in the usual-care group, with an odds ratio of 1.15 (95% CI, 0.81 to 1.65), indicating no significant difference in mortality between the groups. Another notable secondary outcome was the ability to stand, which was achieved by 77% of patients in both groups, but the median time to standing was 3 days in the early-mobilization group and 5 days in the usual-care group, a difference of -2 days (95% CI, -3.4 to -0.6).

In terms of harms, serious adverse events were reported in 7 patients in the early-mobilization group and in 1 patient in the usual-care group. Adverse events that were potentially due to mobilization (such as arrhythmias, altered blood pressure, and desaturation) were reported in 34 of 371 patients (9.2%) in the early-mobilization group and in 15 of 370 patients (4.1%) in the usual-care group, resulting in a p-value of 0.005, which indicates a significantly higher rate of these adverse events in the early-mobilization group

Regarding the process of care, including the use of tracheostomy, neuromuscular blockers, glucocorticoids, new renal-replacement therapy, reintubation, and vasopressor-free days, no significant differences were noted between the groups.

Adverse events potentially due to mobilisation were more common in the early-mobilisation group (9.2%) compared to the usual-care group (4.1%). Most of these events were cardiac arrhythmias, altered blood pressure, and oxygen desaturation. Eight serious adverse events were reported, with seven in the early-mobilisation group and one in the usual-care group. All these serious adverse events necessitated medical intervention, with one cerebrovascular accident in the early-mobilisation group resulting in persistent unilateral weakness. There were no reports of patients falling, cardiac arrests, unplanned extubation, or urgent intravascular line replacements.

Critique

TEAM was an impressive international collaboration to address an important topic which has long proven attractive to researchers. The trial had numerous strengths, including its large size, with 750 patients, and broad applicability, due to centres across 6 countries, increasing the generalisability of the findings. The primary outcome was at 6 months, a significant period of time for mobilisation in the ICU to have projected an effect on

recovery. This prolonged primary outcome also permits other interventions, such as ward based rehabilitation and mobilisation, to have an effect. It may be that the early gains are simply lost when a patient returns to usual care and leaves the rigours of a major trial.

The nature of the intervention also led to some limitations. The open nature of the trial could bias healthcare staff to modify their behaviour. The control group received the usual care delivered at their centre, leading to the potential for heterogeneity across the control arm. Despite this, the groups separated well, with the intervention group having 12 more minutes of mobilisation per day. Notably, the control group also achieved a higher level of mobilisation than in other trials, perhaps making the TEAM trial almost too good. It is possible the control group received a more optimal amount of mobilisation, more than in previous trials, but less than the intervention in this trial.

There was no significant difference in the primary outcome (days alive and out of the hospital at 180 days) between the early mobilization and usual care groups. This suggests that early mobilisation might not significantly improve this particular outcome for ICU patients undergoing mechanical ventilation. However, rehabilitation on the ward and other practices

However, the trial did find that patients in the early mobilisation group were able to stand sooner than those in the usual care group, which might imply some functional benefits of early mobilisation. On the other hand, there was a significantly higher rate of adverse events potentially due to mobilisation in the early mobilisation group, suggesting that this approach might entail some risks.

This doesn't necessarily mean that early mobilization is harmful per se, but it might indicate that certain patients or situations require more caution when implementing early mobilisation than is currently practised. The recorded adverse events suggest early mobilisation may have negatively and destabilised patient’s cardiovascular or respiratory systems, leading arrhythmias, altered blood pressure, or desaturation. No patients fell during the trial, which was a commendable effort given he lengths teams went to mobilise patients.

The burning question TEAM forces is whether early mobilisation is harmful and our evolutionary response to being unwell, lying down, should be observed more. Analogous to the presumption that critically ill patients must eat, while our evolutionary response is to develop anorexia, it is thought-provoking to reflect upon the potential harm from early feeding. No doubt the TEAM trial will spur efforts to identify the Goldilocks zone of not too much and not too little mobilisation.

Body of Evidence

Moss and colleagues[7] compared an intensive physiotherapy (PT) program with a standard-of-care PT program in patients who required mechanical ventilation for at least 4 days. These patients were randomized to receive PT for up to 4 weeks, delivered in either an intensive or standard-of-care manner. The primary outcome was the Continuous Scale Physical Functional Performance Test short form (CS-PFP-10) score at 1 month. 120 patients were enroled from five hospitals. The intensive PT group received significantly more physiotherapy, with an average of 12.4 ± 6.5 sessions totalling 408 ± 261 minutes, while the standard-of-care group received an average of 6.1 ± 3.8 sessions totalling 86 ± 63 minutes. Physical function assessments were available for 86% of patients at 1 month, 76% at 3 months, and 60% at 6 months. While physical function was reduced in both groups, it showed significant improvement over time at 1, 3, and 6 months. However, there were no significant differences between the two interventions in terms of the total CS-PFP-10 scores at all three time points (P = 0.73, 0.29, and 0.43, respectively) or in the total CS-PFP-10 score trajectory (P = 0.71). Thus, the results suggest that while the intensive PT program resulted in significantly more therapy time, it did not lead to significant improvements in physical functional performance compared to the standard-of-care PT program.

EPICC[8] was a randomised, parallel-group, allocation-concealed, assessor-blinded, controlled trial, investigating the effects of physical rehabilitation in patients who had received at least 48 hours of either invasive or non-invasive ventilation. The study included 308 participants, recruited over a span of 34 months. Participants were divided evenly, with 150 assigned to the intervention group and 158 to the control group. The intervention group had a target of 90 minutes of physical rehabilitation per day, while the control group had a target of 30 minutes per day. Both groups were scheduled for rehabilitation from Monday to Friday. The primary outcome was the Physical Component Summary (PCS) measure of the SF-36 at 6 months. In terms of the amount of physical rehabilitation received while in the ICU, the intervention group had a median of 161 minutes (interquartile range, or IQR, 67-273 minutes), compared to 86 minutes (IQR, 31-139 minutes) in the control group. However, at the 6-month mark, the number of participants contributing primary outcome data had dropped significantly. In the intervention group, 62 participants contributed data, while 43 had died, 11 had withdrawn, and 34 were lost to follow-up. In the control group, 54 participants contributed data, while 56 had died, 5 had withdrawn, and 43 were lost to follow-up. Despite the intervention group receiving more physical rehabilitation, there was no difference in the primary outcome at 6 months. Both groups had a mean PCS score of 37, with a standard deviation of 12.2 in the intervention group and 11.3 in the control group. This suggests that the increased amount of physical rehabilitation in the intervention

group did not result in improved physical function as measured by the PCS of the SF-36 at 6 months.

Morris and colleagues undertook a single-centre, randomized clinical trial comparing standardized rehabilitation therapy (SRT) to usual ICU care in patients with acute respiratory failure. The study included 300 adult patients (mean age 58 years, 55% women) who required mechanical ventilation. They were equally divided into two groups: the SRT group (n=150) and the usual care group (n=150). The study was conducted from October 2009 through May 2014 with a follow-up period of 6 months. The SRT group received daily therapy until hospital discharge, consisting of passive range of motion, physical therapy, and progressive resistance exercise. The usual care group received weekday physical therapy when ordered by the clinical team. The median days of delivery of therapy for the SRT group were 8.0 for passive range of motion, 5.0 for physical therapy, and 3.0 for progressive resistance exercise. The usual care group had a median of 1.0 days of physical therapy delivery. The primary outcome of the study was hospital length of stay (LOS). Secondary outcomes included ventilator days, ICU days, Short Physical Performance Battery (SPPB) score, 36-item Short-Form Health Surveys (SF-36) for physical and mental health and physical function scale score, Functional Performance Inventory (FPI) score, Mini-Mental State Examination (MMSE) score, and handgrip and handheld dynamometer strength. There was no significant difference between the two groups for the primary outcome, median hospital length of stay (10 days for both groups), or in secondary outcomes including duration of ventilation, or ICU care. At the 6-month mark, no significant effects were seen on handgrip strength, handheld dynamometer strength, SF-36 physical health score, SF-36 mental health score, or MMSE score. However, the SRT group scored higher at 6 months for the SPPB score, SF-36 physical function scale score, and the FPI score, ($P = 0.04$ for SPPB score, $P=0.001$ for SF-36 physical function scale score, and $P=0.02$ for FPI score), suggesting that SRT may have beneficial effects on these aspects of physical function in patients with acute respiratory failure.

In a multicentre, international, randomized controlled trial conducted in Surgical Intensive Care Units (SICUs) of five university hospitals in Austria, Germany, and the USA, Schaller and colleagues investigated the effects of early, goal-directed mobilisation in comparison to the standard of care.[9] The study enrolled patients aged 18 years and older, who had been mechanically ventilated for less than 48 hours and were expected to require mechanical ventilation for 24 hours or more. Patients were randomly assigned in a 1:1 ratio to either standard care (control group) or early, goal-directed mobilization (intervention group). The latter used an inter-professional approach of closed-loop communication and the SICU optimal mobilization score (SOMS) algorithm, which rates patients' mobilization capacity on a scale from 0 (no mobilization) to 4 (ambulation). The

main outcomes tested were the mean SOMS level achieved during the SICU stay (primary outcome), patient's length of stay in the SICU, and the mini-modified functional independence measure score (mmFIM) at hospital discharge (both secondary outcomes). The study took place between July 1, 2011, and Nov 4, 2015, and involved 200 patients (96 in the control group and 104 in the intervention group). The intention-to-treat analysis revealed that the intervention group experienced improved mobilisation (mean achieved SOMS of 2.2 in the intervention group vs. 1.5 in the control group), decreased SICU length of stay (mean 7 days in the intervention group vs. 10 days in the control group), and improved functional mobility at hospital discharge (mmFIM score of 8 in the intervention group vs. 5 in the control group). Adverse events were more common in the intervention group (25 cases, 2.8%) than in the control group (10 cases, 0.8%), though no serious adverse events were observed. Mortality rates were slightly higher in the intervention group both before hospital discharge (16% vs. 8% in the control group) and 3 months after hospital discharge (22% vs. 17% in the control group).

Schweickert and colleagues[10] undertook a dual-centre randomised controlled trial in 104 critically ill adults and compared early exercise and mobilization (physical and occupational therapy) during periods of daily interruption of sedation (intervention group; n=49) or to daily interruption of sedation with therapy as ordered by the primary care team (control group; n=55). The primary endpoint was the number of patients returning to independent functional status at hospital discharge. 59% of patients in the intervention group returned to independent functional status at hospital discharge, compared to 35% in the control group (odds ratio 2.7, p=0.02). The intervention group also had a shorter duration of delirium (median of 2.0 days vs 4.0 days in the control group, p=0.02) and more ventilator-free days (23.5 days vs 21.1 days in the control group, p=0.05) during the 28-day follow-up period. One serious adverse event occurred in 498 therapy sessions (desaturation less than 80%), and therapy was discontinued due to patient instability in 19 (4%) of all sessions, most commonly for perceived patient-ventilator asynchrony.

Paton an colleagues performed a systematic review of randomised clinical trials comparing early active mobilization versus usual care in critically ill adults.[11] 15 trials from 11 countries, and involving 2703 participants, were included. The primary outcome was the number of days patients were alive and out of the hospital by day 180. The pooled data showed a mean increase of 4.28 days alive and out of the hospital for those who received early active mobilisation, although the confidence interval ranged from a decrease of 4.46 days to an increase of 13.03 days. Bayesian analyses indicated a 75.1% probability that the intervention increased days alive and out of the hospital. In terms of secondary outcomes, among survivors, there was a 95.1% probability that the intervention improved physical function as measured through patient-reported

outcomes at 6 months. However, no significant effect was observed for other secondary outcomes. Additionally, there was a 66.4% chance of increased adverse events with the implementation of early active mobilization and a 72.2% chance it increased 6-month mortality.

Should critically ill mechanically ventilated patients routinely undergo early mobilisation

Possibly not. Although the evidence-base is somewhat unclear, there is a worrying signal of potential harm. Further data is required to clarify this.

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Summarising, critiquing and putting into context the best critical care trials of 2022

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