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Targeted Temperature Management After Cardiac Arrest
Finding the Right Dose for Critical Care Interventions

Clifton W. Callaway, MD, PhD

Many clinical trials in critically ill patients do not detect important differences in outcomes between groups receiving different treatments. The trial by Kirkegaard et al[1] in this issue of *JAMA* compared 24 hours vs 48 hours of targeted temperature management (TTM) with cooling to 33°C among 355 patients who were comatose after out-of-hospital cardiac arrest. The investigators found no significant difference in favorable functional neurologic outcome (defined as Cerebral Performance Categories score of 1 or 2) at 6 months for patients treated for 24 hours (n = 176; 64% with favorable outcome) vs 48 hours (n = 175; 69% with favorable outcome) (difference, 5%; 95% CI, −5% to 14.8%). This absence of a dose-effect relationship could cast doubt on the efficacy of TTM, but it also should prompt examination of the core assumptions of dose-finding trials in resuscitation.

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Targeted temperature management changed post-cardiac arrest care. For decades, survival of patients with restoration of pulses after cardiac arrest did not change. In 2002, 2 trials randomized 352 patients after out-of-hospital cardiac arrest and reported improved survival and functional recovery with a package of care that included mild hypothermia (32°C-34°C for 12 or 24 hours) compared with care with no hypothermia.[2,3] Implementation of therapeutic hypothermia, which came to be known as TTM, improved outcomes in many locales,[4] but outcomes worsened with lower adherence to TTM.[5] Most institutions adopted the temperatures (32°C-34°C) and duration (usually 24 hours) used in these early trials.[6] However, no clinical data existed on the optimal depth, timing, or duration of hypothermia. In other words, what was the optimum dose of TTM?

No particular depth of hypothermia is clearly superior for TTM. In a recent systematic review, no superiority was identified for various temperatures from 32°C to 36°C.[7] The largest trial reported similar excellent outcomes for 939 patients after out-of-hospital cardiac arrest who were randomized to TTM at 33°C or at 36°C.[8]

More rapid initiation of TTM is not clearly superior. Six trials found no difference in outcomes for 2379 patients after out-of-hospital cardiac arrest who were randomized to very early, prehospital initiation of hypothermia (<1 hour after arrest) vs later, in-hospital initiation of hypothermia (1-4 hours after arrest).[9] Observational studies of hundreds of nonrandomized patients who received TTM have found no consistent relationship between time-to-target temperature and outcome with early (<4-6 hours) initiation.[10] Preclinical data suggest that TTM initiated after 4 hours is no different from non-TTM treatment.[11] In the trial by Kirkegaard et al,[1] patients had prompt initiation of TTM (<2 hours) and reached target temperature at around 5 hours. The investigators also found no differential effect of TTM duration among patients who reached target temperature within 4 hours after arrest.

Is any duration of hypothermia superior? A systematic review found no interventional clinical data to answer this question.[7] Yet in one preclinical study, 48 hours of hypothermia was superior to 24 hours of hypothermia for reducing neuronal degeneration.[11] It is thus biologically plausible that longer periods of hypothermia may be clinically beneficial. The clinical trial by Kirkegaard et al[1] is the first to explore whether longer durations of TTM improve patient outcomes. This pragmatic trial also made a reasonable assumption that doubling the usual duration of hypothermia to 48 hours was a sufficient dose escalation to detect any signal of benefit while minimizing adverse effects from very prolonged hypothermia.

This trial has many excellent features in its design and conduct.[1,12] Participating centers enrolled more than 98% of

eligible patients following cardiac arrest, patients were randomized individually, treating teams were unaware of allocation until randomization, only 1 individual was lost to follow-up, and more than 80% of patients had prompt coronary angiography. Although it was not possible to blind treating teams to the intervention, assessors for 6-month outcomes were blinded to treatment allocation. In addition, this trial directly addressed the potential bias from withdrawal of life support by providing independent clinicians to conduct multimodal prognostic assessment at least 72 hours after cardiac arrest. This approach has been used in one other large trial,[8] and it should become more standard in all trials of post-cardiac arrest care.

Size is the principal limitation of the trial by Kirkegaard et al.[1] With 355 patients, the study was powered to detect a 15% absolute difference in favorable survival between the intervention groups. However, very few interventions in medicine are that potent, and this effect size is comparable to the original effect of adding TTM to postarrest care.[2,3,7] It is very unlikely that different doses of TTM would affect outcomes as much as the presence or absence of TTM. Nevertheless, this trial does exclude (with 95% CIs) the possibilities that 48 hours of TTM results in a more than 5% decrease in good outcome or a more than 14.8% increase in good outcome. These bounds can guide the design of future trials.

Does the absence of an effect in this trial indicate that duration of TTM does not matter? Combined with the absence of a clearly superior target temperature or a clearly better time of initiation, these data may indicate that dose of TTM does not matter. Alternatively, this trial provides information to help inform the design of other dose-finding trials in resuscitation.

First, power calculations should be realistic and try to detect clinically important effects. This trial cannot exclude a 5% or 10% difference in good outcome, and such a difference might alter practice. Trials with binary outcomes will almost always require thousands of participants to detect such differences. A systematic review of trials in cardiac arrest from 1994-2014 found only 11 trials that randomized more than 1000 individuals.[13] Continuous measures of outcome rather than dichotomous outcome measures might reduce the required sample sizes.

Second, trials must consider whether ancillary care for individual patients overwhelms any intervention effect. Because a team constantly attends to critically ill patients, additional effort might be exerted to improve outcomes for patients allocated to a less efficacious intervention. This influence of medical care will bias the trial toward no difference between groups. Measuring as many ancillary treatments as possible may detect this effect, but there will still be unmeasured confounders given the complexity of intensive care. Regimenting all ancillary care sometimes may be unethical and will always be very expensive. Furthermore, the influence of ancillary care will be greatest in critical care research involving situations in which treating teams constantly adjust therapy, such as duration of ventilator support or dosage of vasoactive drugs. Large pragmatic trials are most prone to bias from medical beneficence, and they may represent a false economy for testing critical care interventions.

Third, dose-finding trials should not assume that there is an optimum fixed dose for the entire population. Analogy to other critical care interventions illustrates how this assumption may be conceptually flawed. For example, in determining the optimal dose of norepinephrine for shock, patients might be randomly assigned to different fixed rates (0.04 μg/kg/min vs 0.1 μg/kg/min), fixed durations (24 hours vs 72 hours), or fixed onsets (immediately on recognition of shock vs within 6 hours of shock.). This approach might identify regimens that are lethal or dangerous, but it would be irrelevant to guiding actual use of a drug that is titrated to individual response. An example of a more relevant trial design would be random assignment to different target blood pressures to which norepinephrine dose is titrated.[14]

Fourth, what are potential targets for titration of TTM? Many basic laboratory experiments have explored how hypothermia reduces molecular events leading to cell death.[15] At a more macroscopic level, hypothermia reduces brain edema, lowers intracranial pressure, reduces frequency of seizures, and lowers brain metabolic need.[16] Intervening with these latter effects may reduce secondary brain injury. Clinicians could titrate temperature to a particular goal based on the response of the patient. For example, a patient with cerebral edema might be maintained at a lower temperature until intracranial pressure is controlled, then rewarmed slowly as long as pressure does not increase.[17] While case series show effects of temperature on individual patient physiology, no trials have compared fixed vs titrated doses of TTM.

In summary, the trial by Kirkegaard et al[1] excludes the possibility that 48 hours of TTM results in outcomes that are 15% better or 5% worse than 24 hours of TTM for good outcomes in patients after out-of-hospital cardiac arrest. However, absence of a superior duration of TTM for the whole population does not exclude the possibility that titration of TTM duration might benefit an individual. Together with other trials, the available data suggest that the benefit from a package of care including TTM is resilient to implementation with a range of target temperatures (32°C-36°C), onsets (0-6 hours), and durations (12-48 hours). Perhaps the dose-effect relationship is flat across a wide range of these doses, or perhaps trials are biased to not detect individual differences. Advancement in resuscitation requires identification of appropriate targets or monitors to guide titration of postarrest care to individual response. Advances may also require more sophisticated trial designs.

ARTICLE INFORMATION

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Interventions to Improve Infant Safe Sleep Practices

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In 2013, there were nearly 3500 deaths among infants from sudden infant death syndrome (SIDS) and other sleep-related events (eg, accidental suffocation) in the United States.[1] Although the cause of SIDS is unknown, several modifiable risk factors have been identified, including prone and side sleep position, bed sharing, and use of potentially hazardous soft bedding in the sleep environment. SIDS rates declined by more than 50% following the Back to Sleep campaign in the 1990s,[2] but since then, rates of sudden unexpected infant deaths have declined less rapidly[1,3] and SIDS remains the leading cause of postneonatal mortality in the United States.[1]

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To improve infant care practices and ultimately reduce SIDS and other sleep-related infant deaths, innovative strategies that educate caregivers about safe sleep and encourage them to adopt recommended infant safe sleep practices need to be developed[3] and their effectiveness evaluated. Effective interventions could be scaled up to reach populations at highest risk and ultimately reduce infant mortality.

A key component to developing effective evidence-based strategies to promote safe sleep is understanding caregivers' barriers to adopting recommendations. Examples of barriers are caregiver concerns about choking risk if an infant is placed supine for sleep[4] or perceived discomfort if the infant is not placed in a warm and soft environment with blankets and pillows.[5] With an understanding of the barriers, interventions can be developed to counteract them.

In this issue of *JAMA*, the Social Media and Risk-Reduction Training (SMART) randomized clinical trial evaluated 2 such strategies: a nursing quality improvement (NQI) intervention provided postpartum teaching and modeling to mothers during the postpartum hospital stay, and a mobile health (mHealth) intervention delivered tailored email or text messages and videos to mothers up to 60 days after giving birth.[6] The safe sleep interventions encouraged supine sleep position, room sharing without bed sharing, not using soft bedding in the sleep environment, and pacifier use when placing the infant to sleep for naps and at bedtime. In addition, the safe sleep mHealth messaging aimed to counteract barriers that can limit use of safe sleep practices. Control interventions substituted breastfeeding for safe sleep practices.

Sixteen US hospitals were selected from a nationally representative sample of 32 hospitals with more than 100 deliveries annually, based on their history of successful recruitment for the Study of Attitudes and Factors Effecting Infant Care Practices (SAFE) study.[7] Hospitals were randomly assigned to 1 of 4 intervention combinations: breastfeeding NQI