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Targeted temperature management after cardiac arrest due to drowning: *Frequentist* and *Bayesian* decision-making

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Now, whenever we care for comatose survivors of out-of-hospital cardiac arrest (OHCA) we must decide the target for body temperature. Whether to select normothermia or hypothermia as the target in pediatric cases was recently reviewed by the International Liaison Committee on Resuscitation (ILCOR) and the American Heart Association (AHA) (1,2). The recommendations (Class IIa, moderate; level of evidence B-*Randomized*) provide us with two choices: 1) 5 days of targeting temperature 36°C to 37.5°C (normothermia), or 2) 2 days of targeting temperature 32°C to 34°C, followed by 3 days of normothermia.

Which temperature strategy in comatose survivors of OHCA?

To date, there are two randomized clinical trials (RCT) of targeted temperature management (TTM, 33°C versus ~36°C) in comatose survivors of OHCA; one in adult patients (3), and the other in pediatric patients (4). A conventional “frequentist” meta-analysis using risk ratio (RR) of death across the studies as the effect measure to compare hypothermia and normothermia therapy shows a pooled estimate with a random effects model to be 0.96 (95% confidence interval [CI] 0.82–1.12, $p=0.59$; Figure 1A; see online appendix for methods). These findings indicate equal effect; hence, no apparent guidance as to what TTM strategy to use in an individual patient.

Any special circumstances that favor one TTM strategy over the other?

In this issue of the *Journal*, Moler et al. (5) consider the special circumstance of TTM in pediatric comatose survivors of OHCA due to drowning. Drowning comprised 28% of the landmark pediatric TTM (33°C versus 36.8°C) RCT (4) and we now have an analysis of these 74 cases. The authors' principal observation is that targeting hypothermia, as compared with targeting normothermia, did not result in better survival (5). Even though a negative

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result from this *post hoc* “exploratory” analysis is expected (6,7) given the design and results of the main RCT (4), the findings will impact future management of pediatric drowning.

The 2010 and 2015 updates in *Pediatric Advanced Life Support* guidelines for cardiopulmonary resuscitation (CPR) and emergency cardiovascular care said nothing about the TTM strategy in drowning (2,8). However, the new continuous process (i.e., “living website”) for evidence-review (1) means that ILCOR/AHA will evaluate papers close to the time of publication. A potential outcome of the article by Moler et al. (5) is that it will inform guidance on the TTM strategy after OHCA *due to drowning* – albeit likely giving the same choices provided for the care of any comatose survivor of OHCA (see above).

‘Frequentist’ versus ‘Bayesian’ summary of RCTs in decision-making

In the conventional frequentist interpretation of RCTs, the null hypothesis is used to assess the significance of an effect using the effect size, p -value and the CI. The p -value is the probability of observing the effect (or more extreme one) given the null hypothesis (9). The p -value is not the probability that the null hypothesis is true (10). The problem with decision-making based on the p -value is that it can be misleading (11), so instead decision-making is based on effect size and the CI (10). These measures, however, are not sufficient to overcome the main limitation here: this approach does not tell us what we want to know at the bedside. For example, the 95% CI indicates that if the RCT is repeated under the same conditions several times, then 95% of the CIs obtained will contain the true effect size. Rather, what really interests us is the interval that the effect size lies within, with the probability of 95%. Another vulnerability of the frequentist analysis is the potential that extreme heterogeneity within the population will influence the main result (see below). Patients of differing risk stratification are often lumped together and the range in factors within 12-hours of pediatric OHCA, associated with mortality, is an example of this problem (12). The recent reports by Moler et al. (4,5) also describe the same issue. Hence, it is no surprise that pediatric critical care RCTs are rarely definitive (13,14), and summative recommendations need to rely on quality/hierarchical ratings (15).

The “*Bayesian*” approach can be used to calculate probability of any hypothesis given the observed data, which contrasts with the frequentist analysis that assess the probability of observed data given a hypothesis (16). Posterior and prior beliefs are mathematically represented by the probability distributions and the observed data described by a likelihood distribution (i.e., the probability of the observed data conditional on the phenomenon). For example, in the case of TTM for OHCA, the posterior or “current probability” of an effect from hypothermia management in the pediatric study (4) could incorporate the prior probability generated from the RCT in adults (3) (Figure 1B; see online appendix for methods). Alternatively, aggregate statistical assessment can be translated into clinically significant information based on one’s “enthusiasm” or “skepticism” about the use of an intervention (17,18) (see below). Figure 1B shows that after the second RCT of TTM (4), the current probability of reducing mortality with hypothermia compared to normothermia – with $RR < 1$ or relative risk reduction (RRR) $> 0\%$ – is 0.55, which is like tossing-a-coin. However, the current probability or chance of reducing the relative risk of death by 20% or

more when targeting hypothermia rather than normothermia is 1-in-3 (0.34, see RRR>20% curve in Figure 1B).

Making a decision about an individual patient

In everyday practice clinicians are Bayesian decision-makers (10). That said, Bayesian interpretation of RCTs has not gained full acceptance in our community because it requires subjectivity in looking at prior probabilities (17-19).

Now, at the bedside, when we make a choice about the potential benefit of TTM (33°C versus ~36°C) in OHCA we have two RCTs (3,4) and the current report for the specific setting of OHCA due to drowning (5). The report by Moler et al. (5) also shows us that baseline risk – and therefore absolute risk reduction (20) – varies widely in the drowning population; consider the valuable descriptions of outcome in relation to estimated duration of CPR and epinephrine dosing in the current report. (Elsewhere, Moler et al. (12) have described additional factors associated with outcome such as pupil reactivity and minimum pH.) In the clinical setting all of this information and our clinical experience informs our prior belief of whether we think targeting hypothermia would be any different to targeting normothermia. For example, *a priori*, if we believe in only a 1% probability that RRR of death by 20% in our patient (when using hypothermia rather than normothermia as the TTM strategy), then the current probability or chance of reducing the relative risk of death by 20% or more if we actually choose to use hypothermia rather than normothermia is 1-in-6 (0.17). Moler et al. (5) describe the particular features in the patient's history that may lead to this prior belief, e.g., prolonged duration of CPR and many epinephrine doses. Whether we select the normothermia TTM strategy will depend on the balance of potential benefit against potential harm of the intervention. Moler et al. (5) also help us here when they show more frequent culture-proven bacterial infection from blood, respiratory and urine sites in the hypothermia group compared with the normothermia group. What you choose in this balance as you work with a patient's family is “subjective”. And herein lies the criticism.

Taken together, the report by Moler et al. (5) is an important addition to a series of landmark studies (4,5,12). As frequentists we may be tempted to conclude, “yet another negative result”. As Bayesians, however, the information presented about patient severity in the current article (5) informs our prior knowledge in patient care and may be used with our belief during clinical decision-making. Are you suspicious of this approach? We are too, but isn't this subjectivity the meta-cognitive landscape that clinicians navigate everyday? At least we now have a framework and data!

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1. **A**, Conventional frequentist analysis of hypothermia mortality risk ratio in two TTM RCT (hypothermia [HT] versus normothermia [NT]). **B**, Bayesian analysis of hypothermia versus normothermia (RRR, relative risk reduction). See online appendix for methods and text for details.