Therapeutic Hypothermia in Children

To the Editor: Moler et al. (May 14 issue)1 report that in comatose children who survived out-of-hospital cardiac arrest, therapeutic hypothermia did not confer a significant benefit in survival with a good functional outcome at 1 year. Two issues concern us about rejecting such therapy.

First, accounting for the presence of pupillary responses at presentation may influence the analysis. Moler et al. previously found that bilateral reactive pupils up to 12 hours after the return of circulation were independently associated with lower mortality.2 The current study did not present this information.

Second, a Bayesian approach may show a significant reduction in mortality and morbidity among younger patients. The current study showed a trend toward statistical significance and a significant difference in the time to death. Neonatal studies have shown that among infants with hypoxic–ischemic encephalopathy, therapeutic hypothermia is associated with a 25% reduction in the rate of death or severe neurodevelopmental impairment.3 Thus, we speculate that reanalysis with the use of a Bayesian statistical approach4,5 that accounts for prior probabilities from neonatal trials involving younger patients may show an effect. For older patients, prior probabilities from trials of therapeutic hypothermia involving adults may be used, with sensitivity analyses for patients of intermediate age.

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To the Editor: In this challenging, multicenter, randomized study of the use of therapeutic hypothermia in comatose children after cardiac arrest, 1355 patients were screened for eligibility, and 260 patients had data that could be evaluated for the primary outcome, 1-year survival with a Vineland Adaptive Behavior Scales, second edition, score of 70 or higher (on a scale from 20 to 160, with higher scores indicating better function). Conclusions from this study are hampered by its limited power. It was designed to detect an absolute survival difference of 15 to 20%, assuming a survival rate of 15 to 35% among patients in the normothermia group, with a power of 85%. Under these overly optimistic and unfounded conditions and despite pertinent literature,1-3 the authors estimated that only 276 patients would be needed. An absolute difference of 8 percentage points in the primary outcome, however, which still corresponded to a relative increase of greater than 50% in neurologically acceptable survival, and a P value of 0.14 strongly suggest that the study was severely underpowered (42%) to rightfully reject the null hypothesis under these conditions.

Therefore, it would be premature to conclude that withholding therapeutic hypothermia from pediatric patients does not make a difference in outcome. An increase in survival of greater than 50%, though not significant because of a suboptimal study design, points in a very different direction.

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THE AUTHORS REPLY: We found that therapeutic hypothermia, as compared with therapeutic normothermia (another active intervention), did not result in a significant benefit. Clinicians may decide that either intervention is reasonable, since we did not find treatment differences and adverse effects were similar.

In reply to the comment by Geva and colleagues regarding pupillary response: the residual effects of atropine and epinephrine on pupils and the requirement of expeditious enrollment less than 6 hours after the return of circulation complicated the use of this measure. Instead, site clinicians who were familiar with the patients determined whether limitations associated with treatment made them ineligible for enrollment. Geva and colleagues suggest that Bayesian analyses that account for prior treatment-effect distributions from other trials could be used to interpret the results. Findings of such analyses are highly dependent on the subjective determination of prior distributions. For example, it is debatable whether the results in a population of newborns with hypoxic–ischemic encephalopathy are relevant to older populations with cardiac arrest, and the way in which other study-specific factors should “weight” the relative importance of other trials in a prior distribution is similarly subjective.

Riess and colleagues note the high power to detect a significant treatment effect in our trial, assuming a 15 to 20% absolute benefit with respect to the primary outcome. Although our results allow a post hoc ruling out of 20% benefit, the trial cannot be retrospectively viewed as suboptimal or flawed because of its negative findings. The P value of 0.14 only indicates that 14% of the time, if there is truly no difference between two treatments, a trial of this size will by chance observe a difference of 7.3 percentage points or more in favor of one treatment. Thus, we cannot defend this 7.3-percentage-point difference, which is not statistically significant, as being a trend, and our trial is a conclusively negative trial when analyzed as intended. The references cited by Riess and colleagues are not very relevant, since they included patients who did not survive to 6 hours after admission. Relevant information was collected in our pretrial cohort study at sites that later participated in our trial. A detailed article about our primary outcome selection and sample-size calculations describes the effect sizes that were based on the published results of neonatal and adult hypothermia trials at the time. Relative risk is associated with major limitations in trial planning and interpretation (e.g., it is identical for 1 vs. 1.5%, 10 vs. 15%, and 50 vs. 75% comparison scenarios). Frank W. Moler, M.D.

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Vasopressin Antagonists

TO THE EDITOR: We disagree with Berl’s discussion, in his review on vasopressin antagonists (June 4 issue), about the availability and adverse effects of urea. First, urea was widely used for many decades — notably, in the United States — to treat conditions other than hyponatremia.