HHS Public Access

Author manuscript

Crit Care Med. Author manuscript; available in PMC 2018 April 01.

Published in final edited form as:

Crit Care Med. 2017 April ; 45(4): 744–745. doi:10.1097/CCM.0000000000002240.

A "Meta-morphosis" in our approach to treatment is not likely to result from a Meta-analysis of the use of therapeutic hypothermia in severe TBI

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Keywords

traumatic brain injury; hypothermia; targeted temperature management; phenotype; cooling; children; pediatric; adult

In this issue of the journal, Crompton et al (1) present a Meta-analysis of the effect of therapeutic hypothermia on outcomes after traumatic brain injury (TBI) in both adults and children. Examining the findings of 42 studies evaluating the effect of the use of therapeutic hypothermia versus standard care in more than 3100 adults and using the same approach in 8 studies of over 450 children, they concluded that the use of therapeutic hypothermia was associated with an 18% reduction in mortality and 35% improvement in neurological outcome in adults. The studies suggested an optimal management strategy of 72 hours of cooling after injury, to a minimum of 33°C, followed by spontaneous "natural" rewarming. In contrast, a 66% increase in mortality rate and a marginal deterioration of neurological come was seen with the use of therapeutic hypothermia versus standard care in children after severe TBI. Overall the authors suggest that therapeutic hypothermia is likely a beneficial treatment following TBI in adults, but cannot be recommended in children.

To date, the greatest benefit of therapeutic hypothermia in critical care medicine has been achieved in the treatment of perinatal asphyxia in term newborns, where numerous high

quality studies have consistently demonstrated beneficial effects on mortality, short and long term neurological outcome, and structural injury on imaging (reviewed in 2). After cardiac arrest in adults, a carefully conducted multi-center study initially suggested benefit from conventional levels of therapeutic hypothermia (3), while more recent studies have suggested that equal benefit might be produced by rigorous clamping of temperature in the patients at 36°C, a strategy often referred to as targeted temperature management (TTM) (4). Whether this approach simply prevents fever or represents a level of ultra-mild therapeutic hypothermia remains to be defined, and is a current area of investigation (5, 6). In children, the recent high quality multi-center therapeutic hypothermia after cardiac arrest trial, although negative for the primary outcome, produced strong trends toward improvements in neurological outcome and mortality despite being fairly underpowered (7). Some have suggested that it in fact supports the use of mild hypothermia (8). Related to all of these studies, in both adults and children with cardiac arrest, state-of-the-art standard of care has in general moved to either the rigorous prevention of fever or the application of mild therapeutic hypothermia (33–34°C) generally for a period of 24–48 hours after the insult—or possibly longer if TTM is utilized.

Despite all of the promise and success of therapeutic hypothermia across the age spectrum in the setting of global ischemic insults such as asphyxia and cardiac arrest and despite suggestion of benefit in a number of single center studies in TBI, a substantial number of the highest quality multi-center studies in both adults and children have failed to demonstrate benefit—and if anything have suggested the possibility of detrimental effects. And paradoxically, the most compelling rigorous multi-center studies carried out to date have suggested a consistently negative and/or detrimental effects in children (9–13).

Many issues make drawing conclusion from a Meta-analysis of studies of therapeutic hypothermia challenging including factors such as the marked heterogeneity in the approaches to cooling, target temperature selected, timing of initiation and duration of cooling, re-warming strategy, inclusion and exclusion criteria for subjects in the studies, and temperature management strategy in the control subjects, not to mention the well-known inter-center differences in background care that is provided (1). Ongoing comparative effectiveness approaches may help us with the latter problem and aid in defining a more consistent optimal approach to standard care (14).

Clearly, in the field of neurocritical care, other than the success of the use of clot retrieval in stroke—where extremely large therapeutic effects on the order of 25–35% versus standard care have been observed (15), the movement in therapy development has been away from a “lumping” approach to one that phenotypes brain injury leading to more highly targeted trials than those carried out to date (16). In the field of severe TBI, this was actually suggested in one of the more recent high quality multi-center randomized controlled trials of therapeutic hypothermia in TBI, where benefit was suggested in the setting of contusion, while lack of benefit and/or detrimental effects were suggested in the setting of diffuse injury (11). It is likely that such an approach in a disease like TBI, where heterogeneity of injury mechanism, anatomic phenotype, genetics, and background therapy for any trial are substantial—and have the potential to reveal clues or even benefits to new therapies. Such a trial is currently underway –where therapeutic hypothermia is being evaluated in adults with

severe TBI and subdural hematoma—to mitigate damage related to ischemia and spreading depression which are mechanisms highlighted in this TBI phenotype (NCT02064959). Unfortunately, meta-analyses of therapies across highly variable approaches in a disease like TBI are unlikely to be informative in this regard.

An interesting finding in this Meta-analysis is the huge divergence in effect of therapeutic hypothermia in adults versus children that was suggested by the analytic approach. If this finding is real, it would contrast the dramatic benefit seen with the use of hypothermia in infants versus a more modest benefit in adults after cardiac arrest. Reversal of this age-related difference would be surprising and difficult to reconcile from the standpoint of biological plausibility. However, there might be several possible explanations including the fact that in pediatric TBI, the continuous infusion of hypertonic saline is an established a ubiquitously used approach—and addition of hypothermia in children may simply reflect a trading of therapies. That was strongly suggested by the work of Hutchison et al (10). It may also be that drug metabolism of agents such as phenytoin is more impaired by hypothermia in children versus adults leading to greater toxicity during rewarming (17) related to drug accumulation.

Finally, based on pre-clinical work, the most compelling findings with hypothermia in TBI have been seen with isolated brain cooling (18, 19) and that approach might represent a new avenue for exploration and with some support from the Meta-analysis—albeit in only 77 patients (1). Thus, we believe that this approach requires further investigation before conclusions can be drawn, but would be logical to consider moving forward particularly in phenotype targeted investigations and/or with the use of new clinical trial designs.

Acknowledgments

Support: This work was supported by an NIH grant T32HD040686 (JSW).

Dr. Kochanek's institution received funding from the National Institutes of Health (NIH), and has received multiple grants from federal agencies including NIH and US Army. He has received funding from Society of Critical Care Medicine (stipend for serving as the Editor-in-Chief of PCCM) and from serving as an expert witness on several cases over the past 36 months. Dr. Kochanek disclosed he has received honoraria for numerous lectures at national meetings and/or as a guest professor at various institutions of higher education. He has also received stipends for editing or authoring books and/or chapters. Dr. Wallisch's institution received funding from NIH T32 HD40686.

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