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ARTICLE OF THE MONTH

Hypothermia for Intracranial Hypertension After Traumatic Brain Injury

Andrews PJ, Sinclair HL, Rodriguez A, Harris BA, Battison CG,
Rhodes JK, Murray GD; Eurotherm3235 Trial Collaborators.
N Engl J Med. 2015 Oct 7. [Epub ahead of print]
PMID: 26444221

This December edition of the SNACC Article of the Month deals with an interesting article which recently appeared in the New England Journal of Medicine. The article by Andrews et al. is truly of interest to any of us who care for TBI patients, whether in the neurointensive care unit, the operating room, or anywhere else, because it sheds more light on an ever-elusive topic: hypothermic neuroprotection. The study itself is a prospective, randomized, multicenter trial comparing therapeutic hypothermia (32-35 degrees Celsius) + standard care *versus* standard care alone for attenuating elevated ICP in TBI patients. The primary outcome was GOS at 6 months, and the result was that hypothermia tended to be detrimental for that outcome. Shedding more light on the article this month is Dr. Sabine E. Kreilinger. Sabine is Assistant Professor of Anesthesiology, Critical Care Medicine and Neurosurgery at the University of Illinois at Chicago. We hope you will enjoy her expert commentary, and please let your thoughts be known via the ***SNACC LinkedIn feed*** the ***Twitter feed***, or the ***Facebook page***. Happy Holidays!.

~John F. Bebawy, MD

Commentary

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Expectations have been high for neuroprotection using therapeutic hypothermia in patients with traumatic brain injury (TBI), although evidence in patients with TBI remained suboptimal. Enthusiasm for therapeutic hypothermia after cardiac arrest was damped by Nielsen et al's study (NEJM), which showed that cooling to 33 vs 36 Celsius had the same results. TBI remains a major cause of death and severe disability and elevated intracranial pressure (ICP) is a marker for poor outcome in brain injury. The Brain Trauma foundation guidelines give a level III recommendation for prophylactic hypothermia in patients with TBI when target temperatures are maintained for more than 48 hours, underscoring the lack of pivotal data.

In the NEJM this past October Andrews et al presented new data on functional outcome after TBI treated with hypothermia to reduce ICP. This study represents the largest international multicenter, prospective, randomised controlled study to date comparing hypothermia and standard care for intracranial hypertension in closed TBI

patients. The Eurotherm3235Trial examined the effects of titrated therapeutic hypothermia (32-35°C) as a treatment for raised intracranial pressure (defined as more than 20mmHg for at least 5minutes after first line treatments with no obvious reversible cause) in closed traumatic brain injury on morbidity and mortality 6 months after TBI. The trial enrolled 387 patients at 47 centers in 18 countries 2009- 2014 who were admitted to the intensive care unit. Eligible patients were randomised to receive either the standard care for patients following traumatic brain injury (first tier of therapy HOB at 30 degrees, CSF drainage, sedation, paralysis, mechanical ventilation) or standard care **with** therapeutic hypothermia (32-35°C). Only centers experienced with the care of TBI patients and the use of hypothermia participated. The primary study endpoint was functional outcome at 6 months. The investigators concluded that both treatment strategies were equivalent in their reduction of ICP, however that the hypothermia group was associated **with higher mortality and poorer functional outcomes.** Extended Glasgow outcome scale (GOS -E) demonstrated an unfavorable outcome at 6 months after injury in the hypothermia group (adjusted common Odds Ratio, 1.53; 95% confidence 1.02 to 2.30; P= 0.04). Favorable outcomes (GOS-E score 5 to 8, indicating moderate disability or good recovery) were found in 49 of 191 patients (25.7%) in the hypothermia group and in 69 of 189 patients (36.5%) in the control group (P= 0.03). Subgroup analysis showed no significant effect between the intervention and prespecified subgroups.

Would the outcome have been different if refractory ICP had been examined?

Unfortunately the investigators did not collect data regarding the quantity of mannitol and hypertonic saline that was administered after failure of controlling ICP with induced hypothermia, nor did they address if hypothermia may have a benefit in refractory elevated ICP. Adverse effects of cooling, such as stress induced decreases in oxygenation of hypoxic areas, coagulopathies, pneumonia and rebound increase in ICP upon rewarming may counteract its neuroprotective effects at this specific stage and beneficial effects of hypothermia may not be seen until further along in the algorithm. This may not be a second tier therapy in TBI patients, but potentially still an option for refractory ICP.

Conclusion

While fever is predictive of worse outcomes in TBI and other neurologic conditions, therapeutic hypothermia led to worse outcomes. Further research may identify specific subgroups that might potentially benefit, or if enforced normothermia is beneficial.