European Study of Therapeutic Hypothermia

The European Study of Therapeutic Hypothermia randomized clinical trial was published in the New England Journal of Medicine. In this study, Andrews et al assessed functional outcomes after traumatic brain injury (TBI) when hypothermia was used as a second-line treatment for elevated ICP. Investigators randomly assigned 387 adult TBI patients in 47 centers across 18 countries with an ICP of >20 mm Hg for >5 minutes despite stage 1 treatments (mechanical ventilation and sedation) to standard treatment (control group) or hypothermia (32°C-35°C) plus standard treatment. In the control group, stage 2 treatments such as hyperosmolar therapy were added as needed to control ICP. In the hypothermia group, stage 2 treatments were added only if hypothermia failed to control ICP. In both groups, stage 3 treatments (barbiturates and decompressive craniectomy) were used if all stage 2 treatments [1)]

The authors found that stage 3 treatments were required to control ICP in 54% of patients in the control group and in 44% of patients in the hypothermia group. Despite these differences, the adjusted common odds ratio for extended Glasgow outcome scale (GOSE) was 1.53 (95% confidence interval, 1.02-2.30; P = .04), indicating a worse outcome in the hypothermia group than in the control group. A favorable outcome (GOSE score of 5-8, indicating moderate disability or good recovery) occurred less often in the hypothermia group (26%) than in the control group (37%; P = .03). Serious adverse events were reported more often in the hypothermia group than in the control group (33 vs 10 events). Study plans originally aimed to enroll 600 patients, but the study was stopped early owing to safety concerns because therapeutic hypothermia plus standard care to reduce ICP did not result in outcomes better than those with standard care alone.

The authors should be commended for carrying out this challenging trial. It is quite difficult to carry out a blinded study in this scenario. Although GOSE assessment was blinded in the present study, assessment of complications during the trial may have been biased because investigators were not blinded. Another drawback is the limited attainment of temperature control, defined as >80% of core temperature measurements within range for days 1 through 4. This was on the lower side in both groups (64.8% in the hypothermia group and 68.8% in the control group). A third potential drawback of the study is that enrollment included patients with TBI resulting from a variety of causes without subgroup analysis. In the National Acute Brain Injury Hypothermia II randomized clinical trial, patients who had surgery for acute subdural hematoma—those most at risk for reperfusion and oxidative injury—had better outcomes.

The investigators in Eurotherm have not presented data on patients with subdural hematomas. Finally, although patients in the hypothermia cohort had better control of ICP, as demonstrated by a decreased incidence of third-line therapies (44% in the hypothermia group, 54% in the control group), therapies such as decompressive craniectomy may confer additional advantages other than just control of ICP.This trial confirms findings of prior studies that hypothermia is not an established neuroprotective agent after TBI and may increase complications. Current therapeutic options in patients with uncontrolled ICPs despite conventional therapies (mechanical ventilation and sedation, hyperosmolar therapy, decompressive craniectomy) remain unclear. Hypothermia is effective in lowering ICP and may be a beneficial final therapeutic option in these refractory cases, but evidence does not support its use in place of conventional therapies [2)].

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Andrews PJ, Sinclair HL, Rodriguez A, Harris BA, Battison CG, Rhodes JK, Murray GD; Eurotherm3235 Trial Collaborators. Hypothermia for Intracranial Hypertension after Traumatic Brain Injury. N Engl J Med. 2015 Dec 17;373(25):2403-12. doi: 10.1056/NEJMoa1507581. Epub 2015 Oct 7. PubMed PMID: 26444221.

2)

Ahmad FU, Starke RM, Komotar RJ, Connolly ES. A Randomized Clinical Trial of Hypothermia as a Preferred Second-Line Treatment for Elevated Intracranial Pressure After Traumatic Brain Injury. Neurosurgery. 2016 Feb;78(2):N10-1. doi: 10.1227/NEU.0000000000001171. PubMed PMID: 26779789.