Experience with prolonged induced hypothermia in severe head injury

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Reports of the use of hypothermia as a treatment for brain injury appeared as early as 1943. Fay [1] cooled a series of patients with severe traumatic brain injury to as low as 28°C for 4–7 days and described outcomes that were, in his view, better than expected. This and subsequent reports did describe several deaths related to cooling, however, presumably as a result of cardiac arrhythmias and sepsis. During the 1960s and 1970s there was little enthusiasm for this treatment because of the general feeling that hypothermia was associated with cardiac arrhythmias, coagulation disorders, and pneumonia.

In the 1980s, however, several investigators demonstrated in the laboratory that mild or moderate hypothermia (32–34°C) was sufficient to cause significant improvement in neurochemical, histologic, and behavioral outcomes in both ischemia and brain injury models, suggesting that beneficial effects could be seen without the side effects that were believed to be associated with lower temperatures. There was a great resurgence of interest in the clinical application of this treatment to patients with stroke and traumatic brain injury. Since 1990, numerous clinical studies have been conducted with the use of mild or moderate hypothermia, primarily in Japan and in the USA. Preliminary reports published in 1993 on patients with traumatic brain injury suggested some benefit with the use of this treatment. In one of the studies [2] hypothermia was used in severely injured patients only after conventional means of control of intracranial hypertension had failed. It was used for as long as 4–5 days and was associated with an increased incidence of pneumonia. In two other studies [3,4] hypothermia was induced as soon as possible after the patient was admitted to the trauma center and was used for 24 or 48 h. In all three studies it was recognized that rapid rewarming of the patients would cause a rebound increase in intracranial pressure, and so gradual rewarming was used.

Most recently, the results of three important clinical trials were published and a multicenter clinical trial was concluded. Schwab *et al* [5] used moderate hypothermia in a series of patients with middle cerebral artery infarction. The patients were cooled to a core body temperature of 33–34°C for 48–72 h, with treatment initiated at a mean of 14 h after onset of symptoms. This was not a randomized clinical trial, but the mortality rate was nearly half that which might have been expected on the basis of historic controls. The investigators did note that pneumonia was a frequent complication and occurred in 40% of their patients. Cardiac arrhythmias were not encountered.

A second study [6] was a randomized trial that evaluated the use of mild hypothermia during intracranial aneurysm surgery. In that study, patients in the experimental group were cooled to 33.5°C only during the surgery for clipping of their aneurysm. The study found that, compared with normothermia patients, more patients with acute subarachnoid hemorrhage in the hypothermia group had good outcomes and fewer of these patients had neurologic deficits at the time of discharge. These differences were not statistically significant, however. There was no apparent benefit of hypothermia for patients who had no preoperative subarachnoid hemorrhage. No significant complications could be attributed to hypothermia as a result of this brief period of cooling (several hours).

The third study and second randomized trial [7] was the study of the use of this treatment for patients with severe traumatic brain injury. In that trial, patients who had an initial Glasgow Coma Scale score in the range 5–7 had significantly improved outcomes at 3 and 6 months after injury if they were treated with therapeutic moderate hypothermia compared with the normothermia group. No benefit was seen for patients who had an initial Glasgow Coma Scale score of 3 or 4. Patients were cooled to 32°C for 24 h in that study.

Finally, a multicenter prospective randomized trial was recently completed and publication of the results is expected early in the year 2000. Briefly, that study found

that therapeutic moderate hypothermia to 32–33°C for 48 h did not lead to significant neurologic improvement for the group as a whole. There was evidence, however, that a subgroup of patients who were aged less than 45 years, were kept normovolemic, and had an initial Glasgow Coma Scale score in the range 5–8 benefitted.

Mechanisms through which this therapy may benefit at least subgroups of brain injured patients include a significant reduction in excitatory amino acids during the period of cooling, and sustained suppression of cytokines, particularly interleukin-1β. Other investigators have identified stabilization of the blood–brain barrier and a general reduction in the post-traumatic hypermetabolic state as other possible beneficial effects of this treatment.

The report of Bernard *et al* in this issue of *Critical Care* [8] is unique in that it critically evaluates the potential side effects of longer term cooling in patients with severe traumatic brain injury. The investigators studied 43 patients with severe traumatic brain injury who were cooled to 33°C for a mean of 8 days and a range of 2–19 days. As has previously been noted, these investigators did find that nosocomial pneumonia was quite common and probably associated with prolonged cooling. They claim a relatively low incidence of fatal sepsis, however (5%). The hypothermia-induced hypokalemia was to be expected and was recognized and treated appropriately. A side effect not previously seen with shorter periods of cooling was thrombocytopenia, and is perhaps the most important side effect that might be related to prolonged periods of therapeutic moderate hypothermia. It is important to note, however, that, as with most of the previous studies, they did not find that cardiac arrhythmias were associated with long-term cooling. Because of the relatively small number of patients enroled in the trial, it is difficult to draw meaningful conclusions regarding the therapeutic efficacy of prolonged hypothermic treatment based solely on that study.

This and other reports, and most especially the multicenter trial of therapeutic moderate hypothermia and traumatic brain injury, indicate that hypothermia is a complicated treatment that is not likely to be beneficial for all patients with stroke, aneurysmal subarachnoid hemorrhage, or trauma. The challenge for future investigators is to identify clearly the select subgroups of patients with central nervous system injury who would benefit. Careful analysis of studies to date clearly indicate that subgroups of these patients will benefit from this treatment, but the multicenter trial also raised concern that other subgroups, such as those head injured patients who are hypovolemic, may actually be harmed by the treatment. Thus, it is premature to offer this therapy as a standard for treatment of stroke or traumatic brain injury patients and the protocols for its use must be carefully worked out, as well as the subpopulations of patients who are most likely to benefit.

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