Neurosurgical forum

as studied by MIB-1 (Ki-67) and PCNA labeling. *J Neuropathol Exp Neurol* 54:776–782, 1995


RESPONSE: I thank Dr. Tang for his interest in our study of VS growth rates in patients with NF2, but some of his comments require clarification. Our study did not test an association between proliferation indices such as Ki-67 and VS growth rates. We reported that VS growth rates in patients with NF2 tended to decrease with increasing age. Proliferation indices do not vary significantly with age in NF2-associated VSs. Therefore, it is unlikely that these proliferation indices alone can explain the age-related change of VS growth rates in patients with NF2.

Dr. Tang’s reference to the results of Abaza, et al., is puzzling. Our study used the same data as these authors, but we reanalyzed their data because there were discrepancies between their results and those of Mautner, et al., who also conducted a longitudinal study of VS growth rates in patients with NF2. After reanalysis, and in contrast to the original report of Abaza, et al., VS growth rates decreased with increasing age and growth rates were not higher in patients with spinal tumors. These results are consistent with those of Mautner, et al.

There are genotype–phenotype correlations for some clinical manifestations of NF2, but two longitudinal studies have not found genotype–phenotype correlations for VS growth rates, which have high intrafamilial variability. Also, monozygotic twins with NF2 have similar general disease severity but differ in specific aspects of their disease course. This suggests that factors other than the type of constitutional NF2 mutation can be important determinants of the disease course of NF2. Examples of such factors are epigenetic effects or stochastic processes such as the timing of the inactivation or loss of the second NF2 allele. Further studies on the natural history of NF2 may provide answers to these questions.

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References


Hypermotera

TO THE EDITOR: We have read with great interest the paper by Shiozaki, et al. (Shiozaki T, Nakajima Y, Taneda M, et al: Efficacy of moderate hypothermia in patients with severe head injury and intracranial hypertension refractory to mild hypothermia. *J Neurosurg* 99:47–51, July, 2003). Because this paper was written by a group that is highly respected in the field of hypothermia research, we believe that the study design and conclusions deserve comment.

Abstract

Object. This study was performed to determine whether moderate hypothermia (31°C) improves clinical outcome in severely head-injured patients whose intracranial hypertension cannot be controlled using mild hypothermia (34°C).

Methods. Twenty-two consecutive severely head-injured patients who fulfilled the following criteria were included in this study: an intracranial pressure (ICP) that remained higher than 40 mm Hg despite the use of mild hypothermia combined with conventional therapies; and a Glasgow Coma Scale score of 8 or less on admission. After the failure of mild hypothermia in combination with conventional therapies; patients were exposed to moderate hypothermia as quickly as possible. As brain temperature was reduced from 34 to 31°C, the volume of intravenous fluid infusion was increased significantly from 1.9 ± 0.9 to 2.6 ± 1.2 mg/kg/hr (p < 0.01), and the dose of dopamine infusion increased significantly from 4.3 ± 3.1 to 8.2 ± 4.4 µg/kg/min (p < 0.01). Nevertheless, mean arterial blood pressure and heart rate decreased significantly from 97.1 ± 13.1 to 85.1 ± 10.5 mm Hg (p < 0.01) and from 92.2 ± 13.8 to 72.2 ± 14.3 beats/minute (p < 0.01) at 34 and 31°C, respectively. Arterial base excess was significantly aggravated from −3.3 ± 4 to −5.6 ± 5.4 mEq/L (at 31°C; p < 0.05). Likewise, serum potassium concentration, white blood cell counts, and platelet counts at 31°C decreased significantly compared with those at 34°C (p < 0.01).

In 19 (86%) of 22 patients, elevation of ICP could not be prevented using moderate hypothermia. In the remaining three patients, ICP was maintained below 40 mm Hg by inducing moderate hypothermia; however, these three patients died of multiple organ failure. These results clearly indicate that moderate hypothermia induces complications more severe than those induced by mild hypothermia without improving outcomes.

Conclusions. The authors concluded that moderate hypothermia is not effective in improving clinical outcomes in severely head-injured patients whose ICP remains higher than 40 mm Hg after treatment with mild hypothermia combined with conventional therapies.

Shiozaki and colleagues have made many clinically relevant contributions to hypothermia research in the field of traumatic brain injury (TBI) in the last decade. Their work has sequentially explored multiple clinical aspects of therapeutic hypothermia. Their paper on the use of mild hypothermia (34°C) to treat high ICP (> 20 mm Hg) refractory to conventional medical treatment and barbiturates was pivotal.
In their most recently published study the authors’ main goal was to show the effects of moderate hypothermia (31°C) in improving the clinical outcome of severely head injured patients with intracranial hypertension that cannot be controlled with barbiturates and mild hypothermia (34°C). The authors concluded that reducing core temperature from 34 to 31°C was not effective in improving neurological outcome in severely head injured patients in whom ICP remained higher than 40 mm Hg after treatment with mild hypothermia (34°C) combined with high-dose barbiturates.

Uncontrollable intracranial hypertension is still the main cause of death in patients with severe TBI. Preclinical and clinical studies have shown the neuroprotective efficacy of moderate hypothermia against brain ischemia and TBI as well as in controlling high ICP; however, the negative results of the National Acute Brain Injury Study on Moderate Hypothermia (prophylactic) in severe TBI (NABISH-1) had serious implications for investigators wishing to continue clinical research in moderate hypothermia. Funding agencies, internal review boards, and regulatory bodies considered the results of the NABISH-1 as a justification for rejecting new proposals for clinical trials of moderate hypothermia. Consequently, any recent study contributing new data on the use of moderate hypothermia is highly important because of its potential to increase or decrease interest in this therapeutic modality. Despite the lack of Class I evidence for the efficacy of moderate hypothermia, a recent survey shows that 41% of the members of the Neuroanaesthesia Society of Great Britain and Ireland induce mild or moderate hypothermia in the management of head-injured patients.

Studies such as that by Shiozaki, et al., are crucial, but their results should be carefully scrutinized. We believe that there are some issues in the study that deserve consideration. These issues affect both patient selection criteria and the therapeutic protocol used. Regarding patient selection criteria, all patients included in their study had severe ICP refractory to first-level therapy at the time of inclusion was between 40 and 80 mm Hg. The ICP threshold used in the study (20 mm Hg) was much lower than that used in the 2003 study. In the 1993 study, mild hypothermia was associated with a huge but marginally significant reduction in the odds of death at 6 months (odds ratio [OR] 0.21, 95% confidence interval [CI] 0.04–1.05) and significantly reduced the odds of a poor outcome (OR 0.1, 95% confidence interval 0.01–1).

In our opinion both experimental and clinical evidence has shown that deferred hypothermia may be an effective method for treating high ICP refractory to first-level therapeutic measures and could be a good alternative to high-dose barbiturates, although this evidence is sometimes conflicting and incomplete. The effectiveness of moderate hypothermia in treating high ICP should be formally proved or disproved in a multicenter randomized clinical trial. No such trial has ever been conducted. To avoid conflicting results and to try to find a definitive answer, however, some conditions have to be fulfilled: 1) appropriate patient selection excluding, as in drug clinical trials, patients in a hopeless clinical situation; 2) a lower threshold of ICP (20–25 mm Hg); 3) homogeneous and strict therapeutic protocols for participating centers to follow; 4) mandatory previous training of the participating centers in inducing and maintaining hypothermia to avoid the failures and mishaps that occur during the learning curve for a difficult therapeutic modality; 5) use of new intravascular cooling methods.

Another issue is the therapeutic protocol used by the authors to manage high ICP. This protocol did not follow the evidence-based recommendations of the Brain Trauma Foundation (BTF) guidelines for the treatment of severe head injuries. Osmotic agents were not used and were substituted by high-dose barbiturates. Although this protocol may be based on the authors’ experience, scientific evidence to support the use of barbiturates over osmotic agents is lacking. Furthermore, no information is provided on the protocol for analgesia and the muscular paralysis algorithm used. These are highly important factors when mild or moderate hypothermia is used to treat high ICP. Even more importantly, and in contrast to the BTF guidelines, a recent systematic review by the Cochrane collaboration has shown that there is insufficient evidence to use barbiturates in the treatment of severe head injury. In the BTF guidelines, barbiturates were accorded the category of Guidelines with the recommendation that they be used as a second-tier measure in patients with high ICP refractory to maximal medical therapy. The Cochrane collaboration found no evidence of improved outcome when barbiturates were used in severe TBI, however. Although high-dose barbiturates may reduce raised ICP, there is no evidence that this reduction is associated with lower mortality rates or improved outcome in survivors. Furthermore, in one of every four patients treated, these drugs lowered mean arterial blood pressure (MABP). The hypotensive effect of barbiturates offsets their beneficial effect in lowering ICP.

Experimental evidence shows the efficacy of hypothermia in controlling high ICP. Interestingly, the only randomized clinical trial in which hypothermia was used to treat refractory high ICP was conducted by the Osaka group. In this trial Shiozaki, et al., randomized 33 patients with high ICP refractory to second-level therapeutic measures, including barbiturates, to mild hypothermia (34°C) by using water-circulating blankets or to a control group in which maximum medical therapy was continued. The ICP threshold used in the study (20 mm Hg) was much lower than that used in the 2003 study. In the 1993 study, mild hypothermia was associated with a huge but marginally significant reduction in the odds of death at 6 months (odds ratio [OR] 0.21, 95% confidence interval [CI] 0.04–1.05) and significantly reduced the odds of a poor outcome (OR 0.1, 95% confidence interval 0.01–1).

With the exception of decompressive craniotomy, all possible therapeutic modalities were used. In this highly restricted group of patients, the predicted outcome would be brain death within a few hours of inclusion. Therefore, it is not surprising that lowering the core temperature by 2 to 3°C had no effect on either ICP or outcome. In our opinion the 22 patients included in this study were in a hopeless situation in which moderate hypothermia was used as a salvage therapy. This point is supported by Fig. 1 in their paper, which shows that basal ICP under maximal medical therapy at the time of inclusion was between 40 and 80 mm Hg. Furthermore, analysis of some data from this study (for example, the mean time between admission and achievement of the target temperature for mild hypothermia) indicates that these patients showed rapid deterioration and early high refractory ICP. Consequently, it would be surprising if moderate hypothermia had been successful in such poor candidates. In view of the patient selection criteria, the 100% mortality rate reported by Shiozaki, et al., seems unavoidable regardless of the therapeutic measures used. Pupil abnormalities at the time of inclusion would have been useful in determining the neurological status of this cohort.