Editorial

Hypertonic saline

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A Thneed’s a Fine-Something-That-All-People-Need!
It’s a shirt! It’s a sock! It’s a glove! It’s a hat!
But it has other uses. Yes, far beyond that.

The Once-ler
from The Lorax, THEODOR GEISEL (DR. SEUSS)

Intracranial hypertension is a life-threatening condition that can arise from a wide variety of neurological disorders, including traumatic brain injury (TBI), stroke, tumor, and infection as well as general medical illnesses, such as hepatic encephalopathy. Local mass effect, vasogenic and cytotoxic edema, inflammation, and blood-brain barrier disruption are among the factors that can lead to brain herniation, permanent neurological injury, and death. Against these forces, the body fights back by raising perfusion pressure to keep the effects of elevated intracranial pressure (ICP) at bay. This is no easy task. In a closed-volume system, pressure rises rapidly once compliance runs out. Physicians enter the fray by attempting to alter the fundamental principle of ICP dynamics described by the Monro-Kellie doctrine, which states that in the fixed cranial space, the brain, CSF, and intracranial blood volume are in equilibrium, in which one cannot be altered without affecting the others. Given the prevalence of intracranial hypertension in TBI, much of the research on treatment of elevated ICP has come from the trauma literature. This research is reflected in the guidelines for the treatment of TBI.1 The mainstay of medical treatment is osmotic diuresis, which has been traditionally accomplished with mannitol, a sugar alcohol that increases the osmolarity of blood, creating an osmotic gradient that pulls free water from the brain, thereby reducing brain volume. Although mannitol is clearly effective in treating many cases of elevated ICP, its use has several drawbacks. Among these are the hypovolemia that occurs as the mannitol is cleared by the kidneys, taking intravascular fluid with it, as well as the interstitial deposition of mannitol over time, which can result in a reverse osmotic gradient. Over the past decade, hypertonic saline (HTS) solutions have emerged as an alternative to mannitol. Increasing the osmolarity of blood with NaCl can establish the necessary osmolar gradient to treat elevated ICP. Hypertonic saline increases blood volume and does not cross the blood-brain barrier as easily as mannitol does, making it a treatment worth investigating.

In their article in this issue of the Journal of Neuro-
surgery, Mortazavi and colleagues2 have written a comprehensive review of 36 papers on HTS therapy and a meta-analysis on the use of HTS versus mannitol for the treatment of intracranial hypertension. This work is an important contribution to the literature for several reasons. It provides a broad overview of the many applications for this novel tool and attempts to demonstrate empirically the utility of HTS for elevated ICP—a great undertaking. An earlier attempt by Ogden and colleagues3 in 2005 faced many of the same issues and could only conclude that HTS therapy was useful, but needed better definition. The literature contains reports that vary greatly in regard to the origin of raised ICP, concentration of HTS used, method of administration (bolus vs drip), study design, and study end points. The authors of the current study use these distinctions to categorize the studies and then examine each grouping, paying special attention to the findings of randomized controlled trials. Although comprehensive, this process is cumbersome. Although the majority of the studies support the hypothesis that HTS is effective at reducing raised ICP, it is difficult to follow the methodology of each individual study. Does the prospective study that looked at HTS boluses in subarachnoid hemorrhage (SAH) use the daily number of episodes of ICP > 20 mm Hg or the 1-year Glasgow Outcome Scale score as a measure of success? However, in the absence of large, randomized studies with standardized end points, the authors’ work is an admirable first step.

In the meta-analysis, the authors pool data from 8 randomized controlled trials that compared HTS with mannitol. Not surprisingly, the definition of failure of treatment is different for each study. Still, combining the studies, the analysis yielded only 19 of 117 failures in patients or episodes in the HTS group compared with 39 of 113 in the mannitol group. Again, it is difficult to draw specific conclusions about the indications and best methods of administration for HTS therapy from this analysis.

Hypertonic saline is an extremely promising treatment for intracranial hypertension. Before we declare that HTS is a fine treatment that all patients need, further study must be done. Although HTS seems to be effective overall, the nuances of its use have not been fully elucidated. Is HTS a better treatment for conditions such as SAH and polytrauma, in which hypovolemia should be avoided, than for other causes of intracranial hypertension? What is the optimal concentration and length of treatment? Finally, and perhaps most importantly, what effects will HTS therapy have on the long-term outcome of patients? Given the frequency of intracranial hypertension in neurological conditions, a great opportunity exists for collaborative research, perhaps starting with an Internet database to collect data (similar to the Hypothermia Network of the International Cardiac Arrest Registry [http://www.hypothermianetwork.com/INTCAR.htm]).
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[Accessed August 17, 2011]) and leading to well-designed, well-powered trials that account for the many complexities of HTS therapy. Unless good studies such as this one are undertaken, we will never find the answers we seek.

Disclosure

The authors report no conflict of interest.

References


Response

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If we knew what we were doing it wouldn’t be research.

Albert Einstein

We appreciate Drs. Hoffer and Selman’s editorial on our study. Their comments support our findings and illustrate what clinicians face in managing intracranial hypertension. It is known that mannitol primarily exerts its effects by making the intravascular compartment hyperosmolar by its own osmotic gradient as well as secondary diuresis, and hence pulls water from the brain along an osmotic gradient toward the intravascular compartment. However, it is not known if the acute hyperosmolarity caused by the mannitol or the secondary hyperosmolarity caused by the osmotic diuresis is the main mechanism of action. If the latter is more important, then one could argue that a hyperosmolar serum, no matter what the agent, has the greatest therapeutic effect. Therefore, anything that would make the serum hyperosmolar would have the same effect. Sodium is the most natural option, although urea has been used in the past.

As Aristotle and Farabi taught, categorization is the key to understanding. Even though the literature is unorganized, it is on the previous attempts of others that our current knowledge is based. As Drs. Hoffer and Selman point out, methodologies are often flawed. For example, mannitol has been used in the first half of a study and HTS in the second half of the study in the same patient cohort. It is obvious that the pathophysiological mechanism of trauma or SAH is distinctly different as time elapses after the event. Also, many studies lack surveillance of serum Na and osmolarity. It is reasonable to assume that HTS, no matter how it is given (drip vs bolus), exerts its effects through alteration of serum Na and secondarily, serum osmolarity. Surveillance of these parameters should be an important part of any well-done trial.

An important point highlighted by Drs. Hoffer and Selman is the utility of HTS or mannitol depending on the source of the intracranial hypertension. Clearly, patients with SAH and the risk for vasospasm need a well-hydrated state compared to those with other sources of intracranial hypertension. At our institution, when mannitol is used for SAH, albumin has been used concomitantly to counteract the osmotic diuresis.

Finally and most importantly, what is the outcome of using HTS and how should it be measured? The duration of raised ICP should be monitored, along with clinical outcomes. This raises the following questions: what is the correlation between length and number of episodes of intracranial hypertension and outcome, and where does HTS stand in relation to this? At this point we do not know; however, these are questions that need to be answered.

We agree with the comments by Drs. Hoffer and Selman on a multicenter clinical study incorporating two experimental cohorts, one using drips and the other using boluses. Mannitol would be the control, and serum Na and osmolarity would be monitored meticulously in all groups.

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