Mannitol versus saline

To The Editor: I read with interest the article by Sakellaridis et al. (Sakellaridis N, Pavlou E, Karatzas S, et al: Comparison of mannitol and hypertonic saline in the treatment of severe brain injuries. Clinical article. J Neurosurg 114:545–548, February 2011). It is a well-known phenomenon that elevated intracranial pressure (ICP) leading to brain herniation is a major cause of death and severe morbidity following brain injury. As well pointed out in Ann-Christine Duhaime’s editorial prefacing the cited article, gains in the treatment of patients with traumatic brain injury (TBI) have been made because of careful attention and the standardization of therapeutic protocols in helping to recognize and minimize further damage and the development of secondary brain insults. A new weapon in such an on-going battle was the recent introduction of hypertonic saline solutions. But it is still unclear which is the better osmotic agent: mannitol or hypertonic saline? By definition, the ideal osmotic agent must be inert and nontoxic, have minimal side effects, and produce strong scientific evidence, the intervention must be evaluated against the aforementioned parameters and not concentrated on a single one, such as ICP alone.

The protocol developed by Sakellaridis et al. initially randomizing similar osmotic burdens of 15% hypertonic saline and 20% mannitol followed by similar alternated osmotic burdens of such solutions, is novel, unique, and well prepared. But a few additional important points must be considered. Despite mentioning that blood pressure, heart rate, ICP, cerebral perfusion pressure (CPP), cerebral oxygenation, hematocrit, PaO2, PaCO2, glucose, osmolality, sodium, potassium, pH, prothrombin time, partial thromboplastin time, and platelet parameters were measured and analyzed, Sakellaridis and colleagues present no detailed statistical analysis of the in-between comparison effect of the alternated dosing for these parameters beyond the effects of reduction and duration of action on ICP. There are no tables, graphs, or any other form of demonstrating the context of the article. Not uncommon in TBI and associated with elevated ICP is decreased CPP, with several degrees of intracranial hypoperfusion leading to hypoxia, ischemia, and metabolic failure. Current standardized protocols for TBI advocate multifaceted management of the main physiological parameters, which include blood pressure, mean arterial blood pressure, ICP, CPP, and brain tissue PO2. To produce strong scientific evidence, the intervention must be evaluated against the aforementioned parameters and not concentrated on a single one, such as ICP alone.

The osmotic mechanism effect of hypertonic saline is different from that of mannitol. Hypertonic saline’s osmotic effect is achieved by drawing fluid from edematous cerebral tissues because it creates a higher concentration of sodium across an “intact” blood-brain barrier. These concentration differences set up osmotic gradients that promote the flow of excess water from cerebral tissue to blood via osmosis. The osmotic movement is associated with a fairly sustained volume-expander effect that is not normally seen with mannitol. Volume expansion can improve blood pressure and CPP. Another attractive property of hypertonic saline is its beneficial effect on cerebrovascular regulation in the brain microcirculation by reducing endothelial cell edema, lowering resistance to flow by improving microvessel diameter.

On the contrary, mannitol’s mechanism of action has been implicated in a plasma-expanding effect that reduces the hematocrit and blood viscosity, increases cerebral blood flow and cardiac output, and improves CPP and cerebral oxygenation. Improvements in cerebral oxygenation induce cerebral vasoconstriction leading to a reduction in blood volume. Mannitol administration decreases CSF production by up to 50%. But the rationale for mannitol’s reduction of ICP is based mostly on its rheological effects. The osmotic effect of mannitol is delayed for 15–30 minutes until gradients are established between plasma and cells. As per hypertonic saline, mannitol’s effects persist for 90 minutes to 6 hours, as demonstrated in several clinical studies. The problem is that once the osmotic gradient is established, increased urine output with associated intravascular volume depletion is the norm. Because mannitol excretion is entirely in the urine, the risk of acute renal failure with an associated hyperosmolar state is more pronounced, as a serum osmolality > 320 mOsm/L is associated with renal and central nervous system effects. Another negative effect of mannitol is related to its reflection coefficient of 0.9; it has the potential of “gapping” endothelial cell junctions and producing a rebound phenomenon, although such conditions are normally seen with repeated doses of mannitol and very seldom with the administration of a single dose.

Hypertonic saline’s basis of benefit in humans remains unclear, and the correlation between serum sodium level and ICP seems contradictory. This may be partially explained by the complex interaction between intravascular volume and serum osmolality. It seems that the hypertonic saline osmotic gradient is directly related to the sodium content in the solution: the higher the sodium concentration, the higher the osmotic effect and possibly the more powerful the action on ICP reduction. The osmolality for a 20% mannitol solution in the cited study is just 1098 mOsm, as compared with 8008 mOsm for a 23.4% hypertonic saline solution. Because of such a
strong osmotic effect, hypertonic saline 23% (bolus administration) is used by many neurosurgical units for the acute management of ICP control. That could partially explain similar findings between the groups in the cited study. It is also important to mention that higher serum sodium with a corresponding higher serum osmolarity (>320 mOsm) seems better tolerated with hypertonic saline than with mannitol.

There is no disputing that the one-on-one comparable effects of mannitol and hypertonic saline on reducing ICP are very similar indeed. The beneficial and repeated effects between the 2 osmotic agents must be evaluated in combination with other important physiological parameters that play a significant role in the management of brain injury and secondary insults. In addition, a graphic analysis of data in the form of tables and graphs could have been included in the authors’ article for better interpretation.

References


Disclosure

The author reports no conflict of interest.

Please include this information when citing this paper: published online October 28, 2011; DOI: 10.3171/2011.3_JNS102010.

Traumatic brain injury or decompression

To The Editor: We read with great interest the article by Ecker et al. (Ecker RD, Mulligan LP, Dirks M, et al: Outcomes of 33 patients from the wars in Iraq and Afghanistan undergoing bilateral or bicompartamental craniectomy. Clinical article. J Neurosurg 115:124–129, July 2011). The authors retrospectively reviewed 33 patients with penetrating traumatic brain injury (TBI) who were treated with bilateral or bicompartamental decompressive craniectomy (DC) during the conflicts in Iraq.
and Afghanistan. They reported that 60% attained a good clinical outcome, 10% remained dependent but interactive, 7% were vegetative, and 23% died. Unfortunately, a recent randomized study (DECREA trial) showed that DC in patients with severe nonpenetrating TBI was associated with more unfavorable outcomes. Patient characteristics and surgical procedures were similar in both the Ecker et al. and the DECREA studies: median age was 24 years, median Glasgow Coma Scale score was 5, and the majority of patients underwent bifrontal or bihemispheric DC. We suppose that, besides differences in study types (retrospective vs randomized), 2 factors at least can contribute to the conflicting results between the 2 studies: 1) differences in the types of injuries, and 2) differences in the timing of DC.

It has been reported that penetrating-blast TBI was the predominant type or mechanism of injury during wartime. Several studies have shown that one of the most frequent secondary injuries of penetrating TBI is cerebral edema, the accumulation of excess water in the brain parenchyma. It has been well known that aquaporin 4 (AQP4), which is one of the main aquaporins in the CNS and acts as a water channel, can contribute to cerebral edema formation. Interestingly, Neal et al. reported that dynamic spatial and temporal changes in AQP4 expression contributed to the molecular pathophysiology of penetrating TBI. Furthermore, we recently reported that DC may affect AQP4 expression and reduce cerebral edema formation after TBI.

Based on these results, DC may improve the outcome of patients with penetrating TBI via the reduction of AQP4 expression. This speculation seems to be parallel to the conclusion by Ecker et al. We think that an ongoing randomized study (RESCUEicp),5 which can include patients with both penetrating and nonpenetrating TBI, may resolve this issue.

Additionally, the median interval from injury to DC was 38 hours in the DECREA trial; however, it might be shorter in the Ecker et al. series. Further investigation about the interval from injury to DC may provide additional insights into studies of DC in patients with TBI.

SATORU TAKEUCHI, M.D.
KOIBO WADA, M.D.
KIMBIRO NAGATANI, M.D.
NAOKI OTANI, M.D.
HIROSHI NAWASHIRO, M.D.
National Defense Medical College
Saitama, Japan

Disclosure
The authors report no conflict of interest.

References

Response: We appreciate the interest and comments of Dr. Takeuchi and colleagues regarding our paper. However, we would like to provide clarity on a few issues. There is actually very little about our patient population that is comparable to the DECREA patients: 1) 100% of the injuries were penetrating head injury—88% from blast injury; 2) all but 3 patients had undergone decompression at the time of initial neurological evaluation; 3) most patients had mass lesions (epidurals, subdurals, or early blossoming contusions) that needed evacuation in addition to the underlying diffuse brain injury; 4) although half of the injuries were bifrontal, all of the operations were tailored, not proscriptive, to the underlying injury; and 5) none of the patients were bilaterally fixed and dilated at the initial evaluation. It should be noted that this series of 33 patients was actually drawn from a larger series of 188 patients with craniectomies over the same time period, therefore making unilateral craniectomy (88%) far more common in the recent conflicts in Iraq and Afghanistan.

We read with great interest the suggestion that Neal and colleagues’ work completed at the Uniformed Services University of Health Sciences, suggesting an increase in the immunoreactivity of the AQP4 channel at 24 and 72 hours in the region of penetrating brain injury, combined with Dr. Takeuchi’s recent work on the AQP4 channel expression being decreased after hemisphericctomy may provide a fluent biophysical hypothesis supporting the use of DC in penetrating head injury. Certainly, more work must be completed in this area. The AQP4 channel seems an excellent target for pharmacotherapeutics.

We too await the findings of the RESCUEicp trial, but in the meantime we fear the misapplication of the DECREA findings to the military and civilian populations. The DECREA population was <5% of the screened patients and is not typical of most military or civilian patients undergoing DC. We hope that the 18 year old with...
the small layering subdural and mass effect out of proportion on the initial postinjury CT scan will still quickly find their way to an operating room for removal of the mass lesion and hemicraniectomy as the brain swelling dictates.

ROBERT D. ECKER, M.D.
Maine Medical Partners Neurosurgery & Spine
Scarborough, Maine
LISA P. MULLIGAN, M.D., CPT, USN
MICHAEL S. DIRKS, M.D., MAJ, USA
RANDY S. BELL, M.D., LCDR, USN
MERYL A. SEVERSON, M.D., CDR, USN
ROBIN S. HOWARD, M.A.
CHRISTOPHER J. NEAL, M.D., LCDR, USN
ROCCO A. ARMONDA, COL, USA
Walter Reed Military Medical Center
Bethesda, Maryland

References

Please include this information when citing this paper: published online November 18, 2011; DOI: 10.3171/2011.8.JNS111351.