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).10 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 establish a strong transendothelial osmotic gradient by remaining largely in the intravascular compartment.17

The protocol developed by Sakellaridis et al.,10 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.2,5,6,11

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.5,6,9,12

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 osmolality (>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.

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Disclosure
The author reports no conflict of interest.

References

RESPONSE: Thank you for your interest in and remarks on our article.

Let us suppose that we treat 2 groups of patients with severe head injury and elevated ICP. We use mannitol for the first group and hypertonic saline for the second. Then, a description and statistical analysis of all parameters that can influence the patient, including blood pressure, mean arterial blood pressure, CPP, and brain tissue PO2, are necessary.

We used a different research model in which the same patient alternatively received mannitol or hypertonic saline of the same osmotic burden. By treating the same patient in consecutive time periods, we could avoid the stratification of multiple independent variables. When one of the variables that we measured changed significantly—for example, PaCO2 diminution in cases of hyperventilation—we formed our pair of events after the therapeutic intervention so that the patient’s parameters were similar during both treatments.

This allowed us to draw clear conclusions about the action of both medications on intracranial hypertension and their duration of action. Cases of patients in shock were excluded from our study. We also accept that mannitol infusion presupposes a well-hydrated patient, but this fact is included in the current guidelines for the treatment of severe TBI. Under these circumstances, we have found that both medications had very similar effects on the diminution of intracranial hypertension and the duration of action. This fact offers strong support to the conclusion that their immediate mechanisms of action on intracranial hypertension are similar.

We are well aware of the proposed differences in their mechanisms of action in general, and we discussed them in our paper. Practically speaking, these differences could have consequences on long-term prognosis. If, for example, one of the medications were safer than the other, it would be preferable, even despite the fact that both were equally effective in lowering ICP. Unfortunately, we did not have groups of patients to compare and consequently we could not answer such questions. Complications in events, as described in our paper, were the same for the two treatments.

Some of these points can be better clarified by also reading the editorial to our article and our response to it. Nick Sakellaridis, M.D.
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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.