EDITORIAL

Advancing the Management of Nontraumatic Brain Injuries with Hypertonic Saline and Mannitol

Rajesh Mohan Shetty

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Introduction

Nontraumatic brain injuries (NTBIs) are a major health problem, and are responsible for significant morbidity and mortality all over the world.[1] Conditions such as spontaneous intracranial bleeding, strokes, infections, tumors, and metabolic abnormalities are classified under NTBIs as they are not the result of direct external forces.[2] Intracranial pressure (ICP) >20 mm Hg and resultant cerebral perfusion pressure (CPP) <60 mm Hg are associated with poor outcomes.[3] Injured brain is vulnerable to increased ICP and this affects the outcome. Therefore, prompt and appropriate reduction of high ICP is crucial.[4]

The effect of osmotherapy has been known since 1919. It was hypertonic saline which was first shown to reduce brain volume in animals by Weed and McKibben.[5] There was no interest in using this in human subjects initially. Mannitol was used for the treatment of intracranial hemorrhage (ICH) for the first time in 1961.[6] It was only in 1988, Worthley et al. showed 30% saline causing a reduction in ICP in two patients, where mannitol had failed when given as a single bolus.[7]

Guidelines vary in relation to their recommendation about the best agent to use for the reduction of high ICP reflecting conflicting reporting from the available literature. The Brain Trauma Foundation 2016 guidelines recommended mannitol for high ICP.[8] The American College of Surgeons Trauma Quality Improvement Practice 2015 guidelines recommended both mannitol and hypertonic saline.[9] The Neurocritical Care Society 2020 guidelines recommend hypertonic saline, however stressed on poor quality of available evidence.[10]

The systematic review and meta-analysis published in the current issue of IJCCM offer crucial insights into the comparative effectiveness of two primary therapeutic interventions for managing elevated ICP in NTBI patients: mannitol and hypertonic saline. This study is both timely and significant, given the ongoing debate regarding the optimal approach for reducing ICP and improving patient outcomes.[11]

Mannitol: A Traditional Approach

Mannitol is not metabolized, not reabsorbed, and excreted by the kidney. Mannitol reduces ICP by lowering blood viscosity. This transiently increases cerebral blood flow and oxygen transport by improving blood rheology. It creates an osmotic gradient across the blood-brain barrier because of its osmotic effect and reduces brain edema. Mannitol reduces ICP within15–30 minutes following administration. The peak effect occurs within 30–45 minutes and lasts for 6 hours. Mannitol has a positive effect on brain metabolism and is neuroprotective as it is a free-radical scavenger.[12]

Department of Critical Care Medicine, Manipal Hospital Whitefield, Bengaluru, Karnataka, India

Corresponding Author: Rajesh Mohan Shetty, Department of Critical Care Medicine, Manipal Hospital Whitefield, Bengaluru, Karnataka, India, Phone: +91 7892193659, e-mail: rajeshshetty@manipalhospitals.com

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For patients with traumatic brain injury, intravenous bolus of mannitol is considered as "gold standard" for the reduction of ICP. Despite its widespread use, mannitol is not without drawbacks. Potential side effects include dehydration, electrolyte imbalances, and renal dysfunction. Furthermore, the risk of rebound intracranial hypertension and its potential to exacerbate cerebral edema due to its permeation through a compromised blood-brain barrier poses significant clinical challenges.[13]

Hypertonic Saline: A Promising Alternative

Hypertonic saline solutions have emerged as a promising alternative, potentially offering superior efficacy in certain clinical scenarios. This study highlights the advantages of hypertonic saline, which works by similarly drawing water out of brain tissue but is suggested to have a lower permeability across the blood-brain barrier. This characteristic may reduce the risk of osmotic shifts that could worsen brain injury, presenting a theoretical advantage over mannitol. However, mechanism of action of hypertonic saline remains controversial. The osmotic effect seems to occur preferentially in the non-injured regions of the brain rather than in the injured regions. Another effect of hypertonic saline may be due to vascular expansion leading to an increase in mean arterial pressure. High mean arterial pressure then causes vasoconstriction if autoregulation of cerebral blood flow is preserved ultimately leading to a reduction in ICP.[14] Advantages of hypertonic saline include in addition to creating an osmotic gradient, it is also an effective plasma expander; it restores resting membrane potentials, stimulates the release of atrial natriuretic peptide, enhances cardiac output, and increases CPP. Hypertonic saline acts faster in reducing ICP and the effect is seen within 5 minutes, but has a longer duration of effect compared to mannitol, effects can last up to 12 hours.[15] Hypertonic saline does not possess a pronounced diuretic effect,

and hence the potential complications of volume depletion and hypotension in contrast to mannitol.[13]

The meta-analysis found that hypertonic saline, particularly in concentrations around 7.5%, often demonstrated superior outcomes in reducing ICP compared to 20% mannitol. However, the safety profile of hypertonic saline, particularly concerning elevated serum sodium levels, requires careful monitoring to avoid adverse effects such as hypernatremia and potential cardiovascular complications. This meta-analysis included studies covering various NTBI conditions such as meningitis, stroke, ICH, etc. Also, seven studies that showed the benefit of hypertonic saline included varied study populations, varying concentrations of hypertonic saline and mannitol, varied modes of delivery (bolus and infusion), and varying endpoints (reduction in ICP, clinical improvement, reduction in mean arterial pressure, etc). Two of the studies were conducted exclusively in children, two of the studies used starch or dextran in addition to hypertonic saline, one study used historical control, not all studies used ICP monitoring and one Chinese study found no difference between hypertonic saline and mannitol but concluded that hypertonic saline should be used as first-line osmotic drug. The validity of combining studies with such heterogeneity is debatable.

Intracranial pressure reduction treatment involves some osmotic component and to compare treatments with different osmolarities ignores this concept. The osmolality of 20% mannitol is 1245 mOsm/kg; therefore, 200 mL provides a 249 mOsm/dose. The osmolality of 7.5% is 2498 mOsm/kg; therefore, a similar volume provides 500 mOsm/dose. Recent studies have shown that 20% mannitol and 7.45% hypertonic saline are equally effective in improving CPP and cerebral blood flow if equimolar and equivolume bolus are given slowly.[16] This was not tested in this study. It is also not clear what is the best target serum sodium level and if bolus or continuous infusions are more useful.

This study did not show any major difference in the side effect profile between the two agents negating any beneficial argument favoring hypertonic saline. It is important to know when a particular hyperosmolar therapy should not be considered. Evidence shows that mannitol should be withheld if sodium is equal to or greater than 155 mmol/L or if the osmolar gap is equal to or greater than 20 mOsm/kg or serum osmolarity is higher than 320 mOsm/L and hypertonic saline should be withheld or stopped if sodium is equal to higher than 155 mmol/L.[17]

Clinical Implications and Future Directions

The findings of this comprehensive review underscore the potential of hypertonic saline as the preferred option for reducing ICP in NTBI patients. However, the study also calls attention to the need for further research, particularly well-designed randomized controlled trials, with equimolar, equivolume hyperosmolar agents in patients with ICP monitoring to establish the long-term safety and efficacy of hypertonic saline relative to mannitol before this evidence can be incorporated into guidelines.

Conclusion

In the management of elevated ICP in NTBIs, both mannitol and hypertonic saline play critical roles. While hypertonic saline shows promise as a potentially more effective treatment with a favorable profile for reducing ICP, further research is essential to confirm these findings and to develop definitive clinical guidelines, especially with regard to various clinical settings, doses, titration goals, and modes of administration (bolus vs continuous infusion). This study marks an important step towards improving patient outcomes in the context of NTBIs, offering valuable insights that could shape future therapeutic strategies.

As the medical community continues to advance in understanding and treating NTBIs, integrating such evidence-based approaches will be crucial in enhancing patient care and mitigating the profound impacts of these debilitating conditions.

Orcid

Rajesh Mohan Shetty https://orcid.org/0000-0002-9426-6701

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