Hyperosmolar Agents for TBI: All Are Equal, But Some Are More Equal Than Others?

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We read with interest the guidelines for the acute treatment of cerebral edema in neurocritical care patients published by Cook et al. [1] and congratulate the authors for their work. Brain edema is a major complication after brain injury, which has a strong association with poor prognosis, and may lead to death if left untreated. We agree with the authors that hyperosmolar agents (hypertonic saline (HTS), mannitol) are cornerstones in its management. However, we do not think the recommendation to suggest a preference for HTS over mannitol to treat cerebral edema in TBI patients is justified. This recommendation is based on very low level evidence, summarized in two meta-analyses [2, 3], where no significant mortality or outcome benefit could be demonstrated in favor of HTS or any other osmotic agent. On the other hand, it is acknowledged that 'the literature suggested HTS was at least as safe and effective as mannitol,' and mannitol is presented as 'also a safe and effective option.' We believe these statements present an inherent contradiction. To support the preference for HTS in their recommendations, the authors refer to 'consistency across the numerous lower-quality studies that HTS was more effective than mannitol for reducing ICP or cerebral edema,' suggesting a potential quicker onset of action, and a more robust and durable ICP reduction for HTS treatment. However, we believe such consistency cannot be claimed, as the (small) study quoted to support this claim [4] has actually compared a HTS/starch combination to mannitol and found that both effectively reduced ICP. While the HTS/starch combination had a statistically significant higher maximum ICP decrease and lower ICP values at 60 min compared to mannitol, it is highly questionable whether these statistical differences have any clinical relevance [4]. The same applies to other solutions such as hypertonic lactate [5]. A European Society of Intensive Care Medicine (ESICM) consensus on fluid therapy in brain injured patients has addressed this question as well [6]. Nine randomized controlled trials (RCTs) were selected comparing mannitol with HTS, representing only low-quality evidence in favor or against specific hypertonic agents [5, 7,8,9,10,11]. The one multicenter observational study that reported potential superiority of HTS (a significantly lower mean daily and cumulative ICP burden in the HTS group compared with mannitol) was graded as very low evidence [12]. The final conclusion of the consensus was that the studies comparing treatment were too heterogeneous and provided too low evidence against or in favor of a specific hyperosmolar agent. A recent Cochrane review came to the same conclusion [13]. A meta-analysis, not considered by the authors of this guideline, compared findings from individual patient data and used random-effects modeling for meta-regression to demonstrate the effectiveness of mannitol for intracranial hypertension. Mannitol was found to be a very

effective agent leading to a consistent reduction in intracranial pressure, and its effectivity was proportional to the degree of intracranial hypertension [14]. HTS use, on the other hand, can expose to an important risk of hypernatremia and osmotic variation [15] compared to mannitol. Since these variations could also be detrimental in some patients, HTS cannot be promoted as being the preferred agent in all brain injured patients.

Therefore, based on the literature, no recommendation suggesting a superiority of one hyperosmolar agent over the other can currently be made, and it appears that both HTS and mannitol have a demonstrated effect on ICP, but not on outcome. We think influential guidelines should not suggest a preference. The choice of a particular hyperosmolar agent can be dictated by circumstances, local availability, or the specific clinical situation of the patient. If both options are equal, one cannot be more equal than the other.

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Conflict of interest

The authors declare that they have no confict of interest.