Treating intracranial hypertension: time to abandon mannitol?

Would you want your brain cells to shrink, and then swell again? Probably not. In this issue of the Journal (page 151), Castillo and colleagues review the effects of mannitol and hypertonic saline on intracranial pressure and the circulation, and ask which should be used to treat intracranial hypertension in intensive care patients. They point out that if intensivists choose mannitol, they can reliably expect their patients’ brain cells to shrink and, not much later, to swell again. Faced with this information, what should intensivists do?

In general, continuous gradual changes in physiological parameters are better tolerated than rapid major changes that occur without counteracting hormonal and physiological responses. Continuous unpredictable variability in physiological parameters is normal as the body maintains homeostasis in the chaotic complexity of critical illness. The absence of any variability (eg, in heart rate) is associated with a dismal outcome. On the other hand, rapid treatment-induced changes in common biochemical variables can be deleterious: for example, a decline in blood glucose level caused by insulin infusion can lead to excessive counter-reactions by hormones such as epinephrine, and rapid correction of hyponatraemia can lead to central pontine myelinolysis. In normal situations, the body repairs organ dysfunction gradually. Therefore, in critical care, continuous slow improvement may be a better option than rapid uncontrolled changes. However, in some life-threatening situations, our current practice is to correct the abnormality more rapidly. This is particularly true when the abnormality causes permanent damage in a time-dependent manner. Acute intracranial hypertension is an example.

Raised intracranial pressure (ICP) is known to permanently damage brain cells over time. Therefore, clinicians act to reduce raised ICP as quickly as possible with any treatment available, including decompressive craniotomy in selected cases. However, all treatments that produce rapid changes in homeostasis also have side effects, and carry limited evidence of safety or efficacy.

Few critical care treatments are based on solid evidence. What is the evidence supporting the use of mannitol to reduce intracranial pressure? Taking into account only studies with a mortality end-point, there is almost none. A recent Cochrane systematic review of the topic comprised only two very small and underpowered trials: one randomised single-blind trial comparing mannitol with placebo in acute traumatic brain injury (deaths, 5/20 v 3/21; relative risk [RR], 1.75; 95% CI, 0.48–6.38), and another comparing mannitol with hypertonic saline (deaths, 5/10 v 4/10; RR, 1.25; 95% CI, 0.47–3.33).

However, we do know that mannitol effectively reduces ICP — at least temporarily. A recent study (not included in the Cochrane review) confirmed that a single equimolar dose of 231 mL of 20% mannitol reduced ICP by 45% of baseline values (−14 mmHg), which was comparable to the effect of 100 mL of 7.45% saline: −35% (−10 mmHg). Two main concerns remain about the use of mannitol, as highlighted by Castillo and colleagues: the effect of disruption of the blood–brain barrier and the reverse osmotic gradient that develops after repeated mannitol doses, possibly leading to rebound increases in ICP.

Although hypertonic saline seems to have an effect comparable to that of mannitol in reducing increased ICP (in equivalent doses), it can also, like mannitol, have side effects. A retrospective study of 107 patients with increased ICP caused by traumatic brain injury or stroke found that a continuous infusion of hypertonic saline (3%) was not associated with an increased risk of infection, renal failure or deep vein thrombosis compared with normal saline, but these effects have all been previously presented as potential side effects of hypertonic saline. In addition, this therapy often leads to hypernatraemia. Logistic regression analysis has shown that severe hypernatraemia in neurological ICU patients is related to excess mortality, but the independent effect of hypernatraemia per se, the exact mechanism, and the safe threshold and ultimate goal in the setting of traumatic brain injury all remain unclear to date. In fact, it has been suggested that hypertonic saline could be safe up to a sodium concentration of 160 mmol/L under careful monitoring. It is noteworthy that other inadequately studied effects of hypertonic saline — including increased chloride load, and changes in intracellular calcium and acid–base balance — may also be clinically significant.

Hypertonic saline has been tested in a moderate-sized randomised trial in patients with traumatic brain injury in the pre-hospital setting. These patients may not have had intracranial hypertension, as the intervention was implemented very early after injury. In this setting, hypertonic saline and normal saline had indistinguishable effects on...
mortality and long-term neurological function. In the critical care setting, in patients with uncontrolled intracranial hypertension, there are no studies comparing hypertonic saline with placebo. However, we recognise that such studies would be considered unethical. Comparisons between hypertonic saline and mannitol are considered ethical and have been reported. The US National Institutes of Health Clinical Trials Registry includes two ongoing studies that compare hypertonic saline and mannitol, but because of their small sample sizes (10 and 50 patients) they will not be able to give definite answers about mortality benefit.\(^{11}\)

Although more than 20 years have passed since the publication of two cases in which hypertonic saline was used to treat intracranial hypertension refractory to mannitol,\(^{12}\) and although mannitol has numerous deleterious side effects, it is still widely used, and the potential superiority of hypertonic saline in terms of mortality is still unproven.

In response to this uncertainty and the evidence suggesting that mannitol and hypertonic saline have equivalent initial effects on intracranial hypertension, the two fluids are probably used almost interchangeably in current Australian and New Zealand critical care practice in patients with refractory intracranial hypertension. However, mannitol has the potential disadvantages of rebound intracranial hypertension and intravascular dehydration. In contrast, hypertonic saline restores intravascular volume, may better maintain central perfusion, and is not associated with any rebound effects. Therefore, despite historical preferences, there is a better rationale for use of hypertonic saline than there is for mannitol.

What should we do? We believe the answer lies not in more random practice, but in more research. This is an important area of ICU research that needs to be tackled with properly designed double-blind randomised controlled trials, first aimed at ICP management and then at changing clinical outcomes. If using saline instead of albumin resuscitation can change outcome in patients with traumatic brain injury, it is conceivable that choosing the correct osmotherapy agent could do the same. We need to find out.

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**References**


