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New Trends in Hyperosmolar therapy?

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Abstract

Purpose of review—discuss trends in the use of osmotic therapy.

Recent findings—use of osmotic therapy has evolved from bolus administration of mannitol to routine use of hypertonic saline (HS) as a bolus as well as in continuous infusions to creating a sustained hyperosmolar state.

In a survey of neurointensivists 55% favored HS over mannitol. Retrospective studies suggest better ICP control with HS. While a prospective study in adults with head injury compared alternating doses of mannitol and HS found no difference in change in ICP control or outcome, two meta-analyses, which did not include this study, favored HS for ICP control (although the absolute difference of 2 mm Hg is of little clinical values) with no difference in outcome.

HS has also been administered by infusions to creating a sustained stable hyperosmolar state. Two studies, using historical controls, suggested benefit of HS infusions. In a prospective, randomized study, in children with severe head injury Lactated Ringer's solution was compared hypertonic saline. Although ICP control was similar, the HS group required fewer other interventions.

Summary—the existing data do not support favoring boluses of HS over mannitol in terms of ICP control let alone outcome. The rationale for continuous infusions to create a sustained hyperosmolar state is open to discussion and use of this approach should be curtailed pending further research.

Keywords

mannitol; hypertonic saline; cerebral edema; intracranial hypertension

Introduction

For decades osmotic therapy has been the keystone of medical interventions used to control elevated intracranial pressure (ICP). In 1919 Weed and McKibben reported that hypertonic fluids could lower intracranial pressure and shrink nervous tissue [1]. Shortly thereafter Fay reported on "the treatment of cerebral trauma, by methods of dehydration" using intravenous hypertonic sodium and magnesium solutions [2]. It was not until the early 1960s, following the introduction of ICP monitoring in head injury, that mannitol came into more widespread use [3,4] and turn into the agent of choice. Recently, hypertonic saline has challenged mannitol's role as the preferred osmotic agent [5]. A recent pro-con debate on osmotic therapy provides a complete summary of the argument for and against its use [6,7].

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Currently, osmotic therapy is routinely used in a wide range of acute conditions. Guidelines recommend its use in head injury [8], ischemic stroke [9], and intracerebral hemorrhage[10]. The literature is rife with studies demonstrating that a single dose of an osmotic agent lowers ICP and improves cerebral perfusion pressure (CPP). Many have compared the effects of mannitol and hypertonic saline on ICP and CPP. However, very little work has been done regarding the impact of repeated dosing, fluid management during osmotic therapy and appropriate clinical targets. Considerable controversy persists regarding the differential effects of osmotic agents on normal and abnormal brain, loss of efficacy over time, and uptake into injured brain. Most importantly, no vogue appropriately designed and powered studies have prospectively addressed the impact of osmotic therapy on outcome.

Despite this lack of knowledge, the indications for and use of osmotic therapy has evolved considerably, primarily driven by opinion and vogue. This has recently led to two major changes in how osmotic therapy is used. First, hypertonic saline (HS) is frequently used as the primary osmotic agent and some argue it should replace mannitol. Second, the approach of using HS infusions to creating a sustained stable hyperosmolar state to prevent or treat cerebral edema and elevated ICP has been introduced into practice.

Physiology of osmotic agents

In order to help evaluate the literature it is appropriate to review the physiology of osmotic agents and how they act.

Osmotic effects

In the body, the administration of an intravenous hypertonic solution creates osmotic disequilibrium (change in osmolality of a solution on one side of a semi-permeable membrane relative to the solution on the other side) between the intra- and extracellular compartments, which are separated by the cell membrane. The extracellular compartment is further divided into the intravascular and interstitial compartments by capillary endothelium. Water moves freely between intra- and extracellular compartments. Water also moves relatively freely across the capillary endothelium, except in the brain where it is limited by the blood-brain barrier (BBB). The net flux of water across the BBB is described by Starling forces. Capillary Hydrostatic Pressure (Pc) and Capillary Osmotic Pressure act in opposite directions across the capillary wall. Hydrostatic Pressure forces act to drive fluid out of the capillary, while osmotic (and to a very small degree oncotic) pressures draw it back.

The tonicity or osmotic effectiveness of a solution depends on both the osmotic gradient created and the osmotic reflection coefficient of the membrane for that solute. Additionally, the low hydraulic conductivity (the ease with which water can pass through a membrane) of brain capillaries must be considered [11,12]. A family of aquaporin receptors appear to play a key role in hydraulic conductivity across the BBB [13]. While water transport through aquaporin channels depends on the concentration gradients across the membrane, changes in permeability of the channels determine the magnitude of the response [14].

It is important to note that the osmotic reflection coefficients across the BBB for mannitol and saline differ, the coefficient for mannitol is 0.9 and that for sodium approaches 1. In pathological states, however, the integrity of the BBB is often disrupted which can result in increased permeability to solutes and increased hydraulic conductivity. The relative degree of each of these changes may differ under different pathological states [15,16].

Brain adaptation to the hyperosmolar state

Frequently, administration repeated doses of mannitol results to a sustained hyperosmolar state. This rise is osmolality is primarily a result of use of isotonic intravenous fluids to

replace urinary losses. Since mannitol promotes excretion free water, administration of isotonic saline leads to an increased osmotic load and a usually a hyperosmolar state [17]. Alternatively, if hypotonic fluids are administered osmolality will likely not rise.

When assessing the effectiveness of an intervention the downstream consequences and the body's response to them must be considered. While the induction of a transient hyperosmolar state may reduce brain water, producing a sustained hyperosmolar state may not be effective due the brain's adaptive response. Movement of water out of the intracellular and interstitial spaces results in brain shrinkage [18]. This change is not static, however, and the brain works to return cell size to normal [19,20]. This is an active process whereby the absolute cellular content of osmotically active particles increases. Elevated osmotic activity within the cells serves to counteract the dehydrating influence of hyperosmolar plasma. Over a few hours intracellular electrolytes rise, followed by a slower accumulation of organic [18] and idiogenic osmoles[20]. The net effect is restoration of cell size with maintenance of the hyperosmolar state. This places limits on the reduction of brain volume that can be expected when the brain is exposed to a sustained hyperosmolar state. Thus any beneficial reduction in brain volume will soon be lost. In addition, this response creates the conditions whereby iatrogenic brain edema may occur if a hyperosmolar state is reversed too rapidly. Thus rapid correction of the hyperosmolar state may lead to rebound cerebral edema when water uptake outpaces the dissipation of the accumulated osmoles[21].

Non-osmotic effects

Because they promote movement of water into the extracellular (and thus intravascular) compartments, mannitol and HS increase systemic blood volume, which leads to hemodilution, increased cardiac output and increased blood pressure. With mannitol, this is rapidly followed by a brisk diuresis, often leading to hypovolemia. HS, on the other hand, is not a diuretic and results in sustained volume expansion, thus giving it a distinct advantage in the setting of hypovolemia.

Mannitol also lowers blood viscosity. This occurs, in part, due to hemodilution, but also by decreasing the volume, rigidity and cohesiveness of red blood cells, thus reducing mechanical resistance [22]. HS also produces hemodilution, shrink red blood cells and increase their deformity [23].

A variety of other effects have been attributed to mannitol and/or HS ranging from free radical scavenging to immune modulation to improved systemic microcirculatory flow occurs through reduced endothelial cell and erythrocyte edema. The certainty and clinical relevance of these effects is unknown.

Mannitol vs. hypertonic saline

Until recently mannitol was the osmotic agent of choice in the US. In the late 1980s there was renewed interest in hypertonic saline [24,25] which has continued to grow over time. An on-line survey of neurointensivists found that 90% reported using osmotic therapy as needed for intracranial hypertension[26]. Practitioners were fairly evenly split between those who preferred HS (55%) and those who preferred mannitol (45%), with some reserving HTS for patients with refractory intracranial hypertension. Those who preferred HS were more likely to endorse prophylactic administration. Recent reports have described the use of hypertonic saline in pediatric patients, compared HS and mannitol in adult head injury, and included two meta-analyses.

Adult head injury

In adults suffering head injury, a prospective comparison between mannitol and HS was performed by Sakellaridis and co-workers [27]. Unlike many prior studies, equi-osmolar doses were used and the effect of repeated doses over a period of time was assessed. The investigators employed an alternating treatment protocol in head injury patients to compare the effects of hypertonic saline and mannitol when administered for episodes of elevated ICP. Doses of similar osmotic load (2 ml/kg of 20% mannitol or 0.42 ml/kg of 15% saline) were administered as a bolus via a central venous catheter. In 199 events occurring in 29 patients the mean decrease in ICP and duration of effect with mannitol and HS were similar (change in ICP: 7.96 mm Hg vs. 8.43 mm Hg, $p = 0.586$; duration: 3 hours 33 minutes vs. 4 hours 17 minutes $p = 0.40$).

A meta-analysis of randomized clinical trials comparing mannitol and hypertonic saline was performed in 2011 by Kamel and colleagues to determine if HS was superior to mannitol for the treatment of elevated ICP [28]. Trials were included if they directly compared equi-osmolar doses of hypertonic sodium solutions to mannitol for the treatment of elevated ICP in patients undergoing ICP monitoring. The primary outcome was the proportion of successfully treated episodes of elevated intracranial pressure. Five trials comprising 112 patients with 184 episodes of elevated ICP were included. Using random-effects models, the relative risk of ICP control favored HS (1.16; 95% CI: 1.00–1.33), and the difference in ICP was only 2.0 mm Hg (95% CI: −1.6 to 5.7). The authors concluded that HS is more effective than mannitol for the treatment of elevated ICP and suggest that hypertonic saline may be superior to the current standard of care.

In a 2012 literature review and meta-analysis was published by Mortazavi et al. [29]. A PubMed search was performed to locate all papers pertaining to HS use for ICP reduction. Of the 36 articles selected, 10 were prospective randomized controlled trials, 1 prospective and nonrandomized, 15 prospective observational trials, and 10 retrospective trials. The authors concluded that available data are limited by low patient numbers, limited RCTs, and inconsistent methods between studies. Yet they concluded that a greater part of the data suggested that HS was more effective than mannitol in reducing episodes of elevated ICP. Of note, the study Sakellaridis and colleagues [27] described above was not included in a prompting letters to the editor questioning the conclusions [30,31].

Pediatric use of hypertonic saline

There has been growing interest in utilization of hypertonic saline in pediatric brain injured patients. Previously, HS use was usually limited to 3% solutions; however, recently the use of 23.4% saline to treat refractory intracranial hypertension children with severe traumatic brain injury was reported [32]. Another pediatric study retrospectively reviewed the use of 3% saline during critical transports over a 4 year period [33]. In that study, 101 children received 3% saline during transport to the hospital; >90% were treated for suspected cerebral edema or intracranial bleeds. Notably, in 96% of cases the initial infusions were administered through peripheral intravenous lines. No local reactions, renal abnormalities, or central pontine myelinolysis were observed.

A very large retrospective cohort study used 8 years of data from the Pediatric Health Information System database to describe the use of mannitol and HS in children with severe traumatic brain injury [34]. Overall, 33% of the 6,238 patients received hypertonic saline, and 40% mannitol. Use of both drugs was independently associated with older patient age, intracranial hemorrhage, skull fracture, and higher head/neck injury severity. Of the 1,854 patients who received hypertonic saline or mannitol for ≥ 2 days in the first week of therapy,

29% did not have intracranial pressure monitoring. Over the course of the 8 years the authors identified a shift toward increasing use of hypertonic saline relative to mannitol.

Continuous infusion of hypertonic saline

As use of hypertonic saline became more widely accepted an approach that had been tried and abandoned with mannitol [35] was applied to HS: the use of continuous infusions. Mildly hypertonic infusions (1.25–1.5% saline) are used in neurocritical units to manage hyponatremia, especially in the patient with subarachnoid hemorrhage. This practice (continuous infusion) was then adapted to the administration of more hypertonic solutions (3.0–7.5%) to treat ICP and cerebral edema.

In a small prospective, randomized controlled trial of fluid management in children with severe head injury, Lactated Ringer's solution was compared to hypertonic saline[36]. Thirty-two children with GCS <8 were randomly assigned to receive either Ringer's solution or hypertonic saline (sodium 268 mmol/L, 598 mOsm/L) for 72 hours. Over time, ICP and CPP did not significantly differ between the groups. However, to keep ICP at <15 mm Hg, the group receiving HS required fewer interventions ($p < .02$). HS patients had significantly shorter ICU stay times (11.6 ± 6.1 vs. 8.0 ± 2.4 days; $p = .04$) and shorter mechanical ventilation times (9.5 ± 6.0 vs. 6.9 ± 2.2 days; $p = .1$). The absolute values of serum sodium and osmolality were not reported, only that they differed between groups; this is of particular interest since the control group received a solution that has a significantly lower sodium content than normal (isotonic) saline. The survival rate and duration of hospital stay were similar in both groups.

In adults, the complications of continuous hypertonic saline therapy were investigated by Froelich and colleagues in a retrospective chart analysis [37]. They reported on 187 patients admitted to a neurosurgical intensive care unit for >4 days with traumatic brain injury, stroke, or subarachnoid hemorrhage, a GCS <9 and elevated ICP or at risk of developing elevated ICP. Based on physician preference, one group was treated with 3% HS infusion at a rate of 1.5 mL/hr/kg body weight as maintenance fluid. The other group received 0.9% normal saline. Two percent saline was used in the HS group during weaning or when sodium was > 155 mmol/L. The incidence of Na >155 mmol/L and Na >160 mmol/L was significantly higher in the HS group. HS infusion was not associated with an increased rate of infection, deep vein thrombosis, or renal failure.

The use of early continuous HS infusion in a cohort of patients with cerebral edema and underlying cerebrovascular disease was retrospectively reviewed by Hauer et al. [38] A heterogeneous group of 100 cerebrovascular patients were treated with continuous infusion of 3% saline. Treatment was initiated within 72 hours of symptom onset at the rate of 12 mL/hr. Plasma sodium and osmolality levels were followed and the infusion rate was adjusted until the targeted plasma sodium level of 145–155 mmol/L and osmolality level of 310–320 mOsm/kg were reached. When the entire cohort was compared to a historical control group of 115 patients with equal underlying disease, those treated with HS had fewer episodes of critically elevated intracranial pressure (92 vs. 167, $p = .027$) and in-hospital mortality was lower (17.0% vs. 29.6%, $p = .037$). However, when each clinical group (ischemic stroke, intracerebral hemorrhage, and subarachnoid hemorrhage) was considered separately, no effect on ICP elevation or mortality was evident. Adverse events, including cardiac arrhythmia, heart, liver or renal dysfunction, or pulmonary edema, occurred in both groups to a similar extent.

In another study Wagner and colleagues treated 26 patients with spontaneous lobar and basal ganglia/thalamic hemorrhage >30 mL with continuous 3% saline infusion initiated within 72 hours of onset. The goal was to achieve serum sodium concentration of 145 to 155 mmol/L

and osmolality of 310 to 320 mOsm/kg [39]. Compared to a historical control group treated with isotonic saline, episodes of elevated ICP or new anisocoria occurred less frequently in the treatment group. In-hospital mortality was 3 (11.5%) in the hypertonic saline group and 16 (25%) in the control group. Side effects including cardiac arrhythmia and acute heart and renal failure occurred in both groups to a similar extent.

A single-center retrospective study of continuous controlled-infusion of HS reported on 50 consecutive TBI patients with refractory intracranial hypertension[40]. 20% saline was infused in order to reach a target sodium level. Infusions were used for 8 (± 4) days. Over that time ICP decreased and CPP increased. No ICP rebound of was reported after stopping the infusion. The main side effect was hyperchloremia. Neither acute kidney injury nor pontine myelinolysis was recorded.

Conclusions

Equi-osmolar boluses of mannitol and HS act in the same way to create an osmotic gradient and reduce brain water and lower ICP. There are conflicting low quality data regarding the equivalence of mannitol and HS. A meta-analysis that favored HS for ICP control found that following bolus administration the difference in ICP was only 2.0 mm Hg, a difference of questionable clinical significance. Great caution should be applied before choosing an agent based on the ICP response to a single bolus; it is important to consider that many other interventions which have had a greater impact on ICP have failed to improve outcome. The relationship between ICP control and outcome has been further challenged by the recent results of a large international randomized trial of treating severe head injury patients with and without ICP monitoring, which failed to show any benefit of ICP monitoring. [41].

An additional argument in favor of HS is its higher refection coefficient across the BBB. However, since most conditions in which osmotic therapy is used are associated with disruption of the BBB this difference may be inconsequential. Thus choice between HS and mannitol should be driven by the characteristics of the agents that differ rather than their similarities, such as their renal effects.

The case for continuous infusion of HS is weaker. The rationale is inconsistent with our understanding of the mechanism of action of osmotic agents. First, the acute osmotic disequilibrium created by a bolus of a hypertonic solution which drives the movement of water out of the brain, is not created when a continuous infusion is used. Second, the creation of a sustained hyperosmolar state by continuous HS infusion drives the brain’s compensatory creation of intracellular osmoles to return cell size to normal. In addition, continuous infusions keep the concentration gradient favoring movement of solutes into the brain, especially in conditions in which the BBB may be damaged.

The clinical studies to date do not provide clear evidence of benefit. The only randomized trial compared HS to a relatively hypotonic fluid. The retrospective studies suffer from selection bias and employ either no or historical controls. The use of continuous infusions to create a sustained hyperosmolar state should be avoided pending further study.

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Abbreviations

HS hypertonic saline

ICP	intracranial pressure
CPP	cerebral perfusion pressure
BBB	blood-brain-barrier
GCS	Glasgow Coma Scale

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Key points

- The minor differences in ICP control between HS and mannitol should not drive decisions about which agent to use.
- The use of continuous infusions of hypertonic saline to create a sustained hyperosmolar state is not consistent with the known physiology.
- Mannitol and hypertonic saline should be administered as boluses and the choice of agent should depend on the side effects of each agent relative to the individual patient's condition.