The Evolution of the Clinical Use of Osmotic Therapy in the Treatment of Cerebral Edema

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Introduction

For decades, one of the primary medical interventions to treat cerebral edema has been the administration of hyperosmolar solutions. The agents used, how they are administered, and the therapeutic targets have evolved considerably over the last century. A review of the process highlights lessons learned, provides insight into current practice, and raises important questions.

Weed and McKibbens [1] were the first to report the ability of hyperosmolar solutions to shrink nervous tissue in 1919. They noted that infusion of a 30 % saline solution produced a marked decrease in brain volume, whereas free water administration resulted in brain swelling. In that same year, Hayden [2] reported a similar effect with 25 % glucose solutions. This was followed by Fay's [3] description of "the treatment of cerebral trauma, by methods of dehydration." Fay initially administered oral hypertonic saline solutions, but because of poor patient tolerance, he switched to intravenous boluses of 15–35 % sodium and magnesium chloride solutions.

Over the next half century, various compounds were investigated, including 50 % glucose, 50 % sucrose, 25 % sodium chloride, 25 % urea, 50 % magnesium sulfate, glycerol, concentrated albumin, and concentrated plasma. Their use was tempered by the caveat that "most of these dehydrating agents have only a temporary effect, which may be followed by a 'rebound phenomenon' during which the intracranial pressure may exceed that which existed before they were administered" [4]. Because of these concerns, osmotic agents were rarely used to treat cerebral edema after the mid-1930s.

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After the introduction of intracranial pressure monitoring (ICP) monitoring to the management of head injury in the1960s, there was a resurgence of interest in the use of osmotic agents. At the same time, mannitol was added to the list of potential osmotic agents [5, 6]. Although initially administered as continuous infusion, the practice of using of intermittent bolus administration evolved rapidly. Mannitol quickly became one of the primary osmotic agents used to treat cerebral edema, primarily because it did not cross the cell membrane, like urea, and was not metabolized, like other sugar solutions. Over time, other concerns about mannitol were noted, including its marked diuretic effect leading to hypovolemia, its association with renal failure, and the identification of "mannitol-resistant" patients.

Hypertonic saline has gained favor because it does not appear to be burdened with these side effects. It has challenged mannitol's position as the preferred osmotic agent [7]. Debates in the literature lay out arguments for and against its use [8, 9]. Additionally, its use has transitioned from administration as a bolus to use as a continuous infusion. This has shifted management to slowly increasing osmolality to a stable high value rather than intermittently and sharply raising osmolality followed by a return to normal levels.

Currently, osmotic therapy is routinely used to treat cerebral edema in a wide range of conditions. Numerous retrospective and prospective series confirm that, in most conditions, a bolus of mannitol or hypertonic saline will lower intracranial pressure, usually to a similar degree. What remains unstudied and poorly understood is the impact of repeated dosing, appropriate fluid management during osmotic therapy, and how to guide therapy. In addition, controversy persists regarding whether osmotic agents act only on normal brain, whether they lose efficacy over time, and whether they leak into the brain. No appropriately designed and powered studies have assessed the impact of osmotic therapy on outcome.

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Physiology of Osmotic Agents

Osmotic Effects

Intravenous administration of a hypertonic solution that is impervious to the cell membrane creates osmotic disequilibrium between the intracellular and extracellular compartments. Water moves rapidly into the extracellular compartment to restore equilibrium. This net shift of water out of the intracellular space results in cell shrinkage.

In the brain, the distribution of osmotic agents is further governed by the blood-brain barrier (BBB), which limits entry of most osmotic agents into the extravascular extracellular space of the central nervous system. The osmotic reflection coefficient indicates the degree to which a solute crosses the BBB; 0 indicating free passage and 1 complete exclusion. Mannitol and sodium are highly excluded by the BBB; the osmotic reflection coefficient for mannitol is 0.9 and that for sodium approaches 1. Yet, in disease states, the integrity of the BBB is often impaired, increasing permeability to solutes as well as increasing hydraulic conductivity.

Hydraulic conductivity (the ease with which water can pass through a membrane) of brain capillaries must also be considered [10, 11]. A family of aquaporin receptors has been identified that appears to play a key role in hydraulic conductivity across the BBB [12]. Changes in permeability of the channels determine the magnitude of the response to osmotic stimuli [13]. Movement of water across the BBB is driven by Starling forces; hydrostatic pressure and osmotic pressure act in opposite directions across the capillary wall, with hydrostatic forces driving fluid out and osmotic pressures pulling it back. The net flux is determined by membrane permeability to solutes (osmotic agents) and solvent (water). The net result of all these factors is described by the tonicity or osmotic effectiveness of a solution, which depends on both the osmotic gradient created and the osmotic reflection coefficient of the membrane for that solute.

Brain Adaptation to the Hyperosmolar State

The beneficial effects of osmotic agents are thought to be the result of their ability to shrink the brain; a single dose of mannitol acutely reduces brain volume by 6–8 % in patients with large stroke and cerebral edema [14]. As this fluid comes from the intracellular compartment, cells shrink, initiating a series of responses targeted at restoring cell size to normal. This process acts in several ways to increase the absolute number of intracellular osmotically active particles to counteract the dehydrating influence of hyperosmolar plasma. Over a few hours, the intracellular content of electrolytes rises, followed by a slower accumulation of organic [15] and idiogenic osmoles [16], which draw water back into the cell. The net effect is restoration of cell size with maintenance of the hyperosmolar state.

This response limits the impact on brain volume that can be achieved when the brain is exposed to a sustained hyperosmolar state. The beneficial reduction in brain volume is lost over time as intracellular osmoles rise. Over 24–48 h, a state is reached where both intracellular and extracellular compartments are hyperosmolar, but cell size has returned to baseline and the reduction in brain volume has been lost. This creates a high risk of rebound edema if osmolality is lowered too quickly. Overly rapid correction that outpaces the dissipation of the accumulated osmoles can have disastrous consequences [17].

Non-osmotic Effects

Administration of any hypertonic solution produces a shift of water into the extracellular (and, thus, intravascular) compartments, increasing blood volume. This leads to hemodilution, increased cardiac output, and increased blood pressure. If the osmotic agent is mannitol, a marked diuresis soon follows, which can lead to hypovolemia and hypotension. Because hypertonic saline is not a diuretic it produces sustained volume expansion, giving it a distinct advantage over mannitol in the setting of hypovolemia.

Mannitol and hypertonic saline also lower blood viscosity. This occurs, in part, as a result of hemodilution but also by decreasing the reducing mechanical resistance of red blood cells, shrinking them, and increasing their deformity [18].

Mannitol and Hypertonic Saline

For decades, mannitol was the osmotic agent of choice in the United States. However, to address some of the possible complications associated with its use, there was renewed interest in hypertonic saline in the late 1980s [19, 20]. The first reports used hypertonic saline to treat “mannitol refractory” patients. Additionally, because, unlike mannitol, hypertonic saline does not have a diuretic effect, it can be advantageous in situations where hypovolemia is a concern, such as in trauma and subarachnoid hemorrhage.

A meta-analysis of randomized clinical trials was performed to determine whether hypertonic saline is superior to mannitol for the treatment of elevated ICP [21]. The selection criteria included only trials that directly compared equiosmolar doses of hypertonic sodium and mannitol in patients

undergoing ICP monitoring. The outcome was based on the ICP response for each dose and did not address repeated doses or patient outcome. Five trials with a total of 112 patients and 184 episodes of elevated ICP were analyzed. Overall, the relative risk of ICP control slightly favored hypertonic saline (1.16; 95 % confidence interval [CI] 1.00–1.33), but the difference in ICP was only 2.0 mmHg (95 % CI: 1.6–5.7), a clinically inconsequential difference. Despite this small difference, the authors concluded that hypertonic saline was more effective and may be superior to the current standard of care.

Another meta-analysis included 36 articles, 10 prospective randomized controlled trials (RCTs), 1 prospective and nonrandomized trial, 15 prospective observational trials, and 10 retrospective studies [22]. The analysis was hampered by low patient numbers, few RCTs, and inconsistent methods among studies. Nevertheless, the authors concluded that a greater part of the data suggested that hypertonic saline was more effective in reducing episodes of elevated ICP.

Hypertonic Saline Infusions

The use of continuous infusions of mildly hypertonic solutions has been introduced as a means of treating or preventing cerebral edema. Solutions of 1.5 % up to 7.5 % sodium chloride or sodium chloride/acetate are infused with the goal of reaching a target sodium concentration. To date, the rationale for this approach has not been clearly elucidated and little is known about its impact. A prospective, randomized controlled trial of fluid management in 32 children with severe head injury compared Lactated Ringer's, a hypotonic solution (273 mOsm/l) to hypertonic saline (598 mOsm/l) [23]. In this small study, ICP and cerebral perfusion pressure (CPP) did not differ between groups; those in the hypertonic saline group required fewer interventions ($P<0.02$) and had shorter ICU length of stay.

Another study retrospectively reviewed the use of early hypertonic saline infusion in a cohort of patients with cerebral edema associated with cerebrovascular disease [24]. A heterogeneous group of 100 patients was treated with continuous infusion of 3 % saline, the rate of which was adjusted until a targeted plasma sodium level of 145–155 mmol/l and an osmolality level of 310–320 mOsm/kg were reached. Compared with historical controls, those treated with hypertonic saline had fewer episodes of critically elevated ICP and lower in-hospital mortality. However, when each clinical entity (ischemic stroke, intracerebral hemorrhage, and subarachnoid hemorrhage) was considered separately, no impact on ICP or mortality was seen.

A continuous 3 % saline infusion was used in 26 patients with spontaneous lobar intracerebral hemorrhage, with a goal serum sodium concentration of 145–155 mmol/l and osmolality of 310–320 mOsm/kg [25]. When compared with historical controls, episodes of elevated ICP or new anisocoria were less frequent in those receiving hypertonic saline. In-hospital mortality was 3 (11.5 %) in the hypertonic saline group and 16 (25 %) in the control group.

The use of continuous controlled infusions of hypertonic saline has been reported in refractory intracranial hypertension [26]. A single-center retrospective study of 50 patients with severe head injury used infusions of 20 % saline to reach a target sodium concentration. Over 8 days of use, ICP decreased and CPP increased. No ICP rebound was reported after stopping the infusion.

Conclusion

Equi-osmolar boluses of mannitol and hypertonic saline act in the same way to create an osmotic gradient and reduce brain water and lower ICP. Data regarding the equivalence of mannitol and hypertonic saline for ICP control after a single dose are conflicting and of low quality. The meta-analysis that favored hypertonic saline for ICP control found the difference in ICP was only 2.0 mmHg, a difference of questionable clinical significance. In addition, the ICP response to a single bolus does not necessarily translate into improved outcome; it is important to consider that many other interventions that 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 results of a large international randomized trial treating patients with severe head injury, with and without ICP monitoring, which failed to show any benefit of ICP monitoring [27].

The case for using continuous infusion of hypertonic saline is weak. The rationale is inconsistent with our understanding of the mechanism of action of osmotic agents. Minimal osmotic disequilibrium is created when a continuous infusion is used. The creation of a sustained hyper-osmolar state by continuous hypertonic saline infusion drives the brain's compensatory creation of intracellular osmoles to return cell size to normal. In addition, continuous infusions maintain a concentration gradient favoring movement of solutes into the brain, especially when the BBB may be damaged.

The clinical studies to date do not provide clear evidence of benefit. The only randomized trial was extremely small and compared hypertonic saline to a relatively hypotonic fluid. The retrospective studies suffer from selection bias and used historical controls. At present, the data do not support the use of continuous infusions of hypertonic solution to treat cerebral edema.

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