Hyperosmolar Therapy for the Intracranial Hypertension in Neurosurgical Practice: Mannitol Versus Hypertonic Saline

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Abstract: Management of cerebral edema and elevated intracranial pressure (ICP) is a critical determinant of patient outcomes. Osmotherapy is the most important options in the medical treatments including controlled ventilation, osmotherapy, maintenance of brain and body homeostasis and sedation. Mannitol and hypertonic saline (HTS) are frequently used among osmotic agents related to brain edema and high ICP. Although mannitol is recommended in guidelines, hypertonic saline seems advantageous over mannitol in many situations, such as providing sustained hemodynamic stability and immunologic effects and less rebound phenomenon. Thus, HTS is emerging as a secure alternative to mannitol in the treatment of intracranial hypertension.

Keywords: Hyperosmolar therapy, Mannitol, Hypertonic saline, Intracranial pressure, Neurosurgery.

INTRODUCTION

Intracranial hypertension and cerebral edema are cardinal manifestations of severe brain injury resulting from diverse insults including traumatic brain injury (TBI), ischemic stroke (IS), intracerebral hemorrhage (ICH), aneurismal subarachnoid hemorrhage (aSAH), infections and neoplasm. Both are recognized contributors to secondary brain injury and to poor neurologic outcomes [1]. Consequently, medical management of cerebral edema and intracranial hypertension is a critical component of perioperative care in neurosurgical practice [2]. The most important options for medical treatment include controlled ventilation, osmotherapy, maintenance of brain and body homeostasis and sedation [3]. Osmotherapy is a cornerstone in neurosurgical practice for TBI, ICH, aSAH and IS [4-7]. Currently, only mannitol and hypertonic saline (HTS) are commonly used for this purpose. Mannitol is widely recognized as the 'gold-standard' for treating intracranial hypertension, but HTS represents a potential alternative that is gaining favor [8]. In this review, we have summarized features of mannitol and HTS, the physiology of osmotic agents and mechanisms of action, experimental trials: mannitol versus HTS and adverse effects.

FEATURES OF MANNITOL

Mannitol, an alcohol derivative of the sugar mannose, was introduced in 1961[9]. Since then, it has remained the major osmotic agent of choices and has been a mainstay therapy in clinical practice for controlling ICP [3]. Currently, it is available 5%, 10%, 15% and 20%. The 15% and 20% solutions are the most commonly used. It is a relatively small molecule with a molecular weight of 182Da, and the 15% solution has an osmolality of 940 mOsml/L. It can not be metabolized by the body and excreted almost completely unchanged in the urine driving strong diuretic effect, which with a half-time of elimination of 1 to 2.5 hours. Mannitol has been given both as continuous infusion and as repeated bolus infusion. Bolus infusion of mannitol seems more effective in reducing ICP than when given as continuous infusion [10]. The recommended bolus dose of mannitol is 0.25 to 1 g/kg body weight [11].

FEATURES OF HYPERTONIC SALINE

Hypertonic saline solution consists of both Na^+ and Cl^- ions with a molecular weight of 58.5Da. The concentration and volume of HTS used are varied significantly, ranging from 1.5% to 23.5% in concentration and 10 to 30ml/kg in volume. Nowadays, a 7.2% solution with small-volume bolus infusion is the most commonly used and continuous infusion of 3% saline is also recommended with less side effects [12]. The 7.2% solution has an osmolality of 2280 mOsm/L and the 3% solution has an osmolality of 950 mOsm/L. This means that 15% mannitol and 3% hypertonic saline are comparable in terms of osmolality. Besides, hypertonic saline is often administrated with oncotic agent such as dextran or HES, which aims at maintaining longer hyperosmotic states.

PHYSIOLOGY OF OSMOTIC AGENTS AND MECHANISMS OF ACTION

In the body, the administration of an intravenous hypertonic solution creates osmotic disequilibrium

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(change in osmolality of a solution on one side of a semi-permeable membrane to the other side) between the intracellular 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. In the brain, water moves relatively limitedly across the capillary endothelium, because of the blood-brain barrier (BBB). Capillary hydrostatic pressure and capillary osmotic pressure act in opposite directions across the capillary wall. Hydrostatic pressure forces act to drive fluid out of the capillary, whereas osmotic pressures draw it back. The osmotic effectiveness of a solution depends on both the osmotic gradient created and the osmotic reflection coefficient of the membrane for the solution. Additionally, a family of aquaporin receptors play a key role in hydrautic conductivity (the ease with which water can pass through a membrane) across the blood-brain barrier (BBB) [13, 14]. Consequently, water transport through aquaporin channels depends on the concentration gradients across the membrane, and changes in permeability of the channels. The reflection coefficient (σ) of a substance reflects the difficulty for the molecule to passively pass through the microvascular wall. This means that the substance is freely permeable at a σ of 0 and impermeable at a σ of 1. It is important to note that sodium has a σ of 1 and mannitol has a σ of 0.9 in normal brain and still less in the injured brain [15]. The integrity of BBB is often disrupted in pathological states, which can result in increased permeability to solutions. This gives the potential for passive transfer of mannitol across the capillary membrane and a rebound increase in ICP after withdrawal of therapy, especially in the injured brain.

Osmotic Effect

Osmotherapy is thought to reduce tissue volume by inducing fluid transfer down osmotic gradients across capillary endothelium and cell membrane. This means that transfer of fluid will occur from the interstitial compartments to the intravascular compartments as long as there is higher osmolality in plasma than in the interstitium, and similarly from the intracellular compartments to the extracellular as long as the extracellular osmolality is higher than the intracellular osmolality. For an intact BBB, the former plays a key role, but the latter also contributes. However, there will be an important mechanism that fluid transfers from the intracellular space if the osmotic agent has passed the cerebral capillaries, which will occur in the location with a disturbed BBB. For example, the osmotic agent will pass through the capillary membrane without hindrance in meningitis [16], where the capillaries are fully and passively permeable to small solutes (σ=0), that is, there will be mainly fluid transfer from the intracellular space to the extracellular space.

Cardiac Effect

Due to promoting the movement of water into extracellular and intravascular compartment, mannitol and HTS increase systemic blood volume, and so increase cardiac output and blood pressure. With mannitol, this is rapidly followed by its strong diuretic effect, often leading hypovolemia. On the contrary, HTS is not a direct diuretic agent [17] and results in sustained volume expansion, thus giving it a distinct advantage in the setting of hypovolemia. In multitrauma patients, hypertonic saline contributes to hemodynamic stabilization and to the prevention of secondary insults.

Microcirculatory Effect

Ischemia associated with trauma affects the endothelia cell membrane, increasing its intracellular volume as a result of water accumulation [18]. An important effect of osmotic agents inducing osmotic fluid shift is the normalization of endothelial cell volume. This increases capillary diameters and reduces resistance to flow. Furthermore, plasma viscosity is reduced as a result of the increased plasma water content [19]. For the HTS, it acts as a relaxant on smooth muscle, which results in arterial vasodilatation, which can offset the vasoconstriction and decrease perfusion caused by the trauma, though the precise mechanism of this effect is unclear [20]. Besides, shrinkage of red blood cells will reduce intravascular brain volume and reduce the rigidity and cohesiveness of erythrocytes [2]. This will alter blood rheology and reduce the viscosity of blood [3, 21, 22] and also improve microcirculation, in combination with the reduced hematocrit.

Immunology Effect

After severe damage, the immune response damages the vessels. Secondary injury is caused by peroxidase and protease-mediated necrosis. Activated leukocytes also cause edema and vasospasm [23]. As reported, mannitol is believed to possess antioxidant effect, but this mechanism and its contribution to patients with high ICP is unclear [13]. HTS represents a comparatively promising solution due to its immunologic properties. HTS decreases migration and

adherence of leukocytes and reduces CD11b expression in both leukocytes and neutrophils [24, 25]. Thus inflammatory side effects are minimized by HTS. Besides, it is noted that HTS reduces pro-inflammatory molecules, such as tumor necrosis factor-alpha (TNF-α), and increases anti-inflammatory cytokines, like IL-ra and IL-10, hence balancing the inflammatory response and avoiding further damage [26]. The data from Coimbra's experiment presented that HTS decreased susceptibility to sepsis after hemorrhagic shock [27] and Charalambous's study showed a considerable reduction in post-operative infection [28], suggesting some clinical relevance of immune-modulatory capacities.

EXPERIMENTAL TRIALS: MANNITOL VERSUS HTS

In the late 1980s, there was renewed interest in hypertonic saline [29, 30]. We reviewed highlighted evidence related mannitol and hypertonic saline during the last decade. For instance, Qureshi and Suarez [31] in 2000 undertook a review on hypertonic saline for the treatment of cerebral edema and elevated ICP. Only case series and small randomized controlled trials (RCTs) from 1965 through 1999 could be analyzed; nevertheless, the authors concluded that hypertonic saline seemed safe and effective for ICP reduction.

A subsequent Cochrane review in 2007 [32] examined mannitol for the lowering of ICP after acute TBI. Nine of the 13 relevant studies had to be excluded from analysis. All of the remaining RCTs not only included a small number of participants but also a different treatment protocol for each. In the final review, only 1 study was included in every category, and evidence was deemed insufficient to make definitive recommendations. Similar conclusions came from another Cochrane review [33] that aimed to examine the effects of mannitol on morbidity and mortality in patients with acute stroke. Only 3 small trials with substantial diagnostic and methodological problems were included; hence, no overall conclusions could be drawn.

In 2009, Oddo M *et al.* [34] involved patients with severe TBI and elevated ICP refractory to previous mannitol and 7.5% HTS administered as second therapy to examine the effects on brain tissure oxygen tension ($PbtO_2$) of the two hyperosmolar solutions. From his study, 7.5% HTS administered seemed associated with a significant increase in brain oxygenation, and improved cerebral and systemic hemodynamics.

Upadhyay *et al.* [35] conducted a prospective randomized study in 2010 to compare the efficacy and side effects of 3% HTS and mannitol in the management of raised intracranial hypertension in 200 children. They concluded that mannitol had several side effects, 3% HTS was a safe and effective alternative in managing cerebral edema by monitoring mean arterial pressure (MAP), coma hours and levels of serum sodium, chloride and osmolality.

A recent Torre-Healy's review [36] in 2011, however, analyzed hyperosmolar therapy for the treatment of intracranial hypertension of different origins. It found that both mannitol and hypertonic saline effectively lowered ICP, with a trend toward better efficacy for hypertonic saline.

A meta-analysis of randomized clinical trials comparing hypertonic saline versus mannitol for the treatment of elevated ICP was performed in 2011 by Kamel [37]. After their analysis of 5 trials (112 patients in total) the authors concluded that hypertonic saline was more effective than mannitol for the treatment of elevated ICP and suggested that hypertonic saline may be superior to the current standard of care.

An recent online survey of neuro-intensivists [38] in 2011 found that 90% reported using osmotic therapy as needed for intracranial hypertension. Practitioners were fairly evenly split between those who preferred hypertonic saline (54.9%) and those who preferred mannitol (45.1%) for patients with refractory intracranial hypertension. Those who preferred hypertonic saline were more likely to endorse prophylactic administration.

Most recently, a literature review and meta-analysis was published by Mortazavi [8]. A PubMed search was performed to locate all papers pertaining to hypertonic saline use for ICP reduction in 2012. Of the 36 articles selected, 10 were prospective randomized controlled trials (RCTs), one prospective and non-randomized, 15 prospective observational trials, and 10 retrospective trials. They concluded that a greater part of the data suggested that hypertonic saline was more effective than mannitol in reducing episodes of elevated ICP. And with regard to short-term neurological outcome, there was a minor positive trend in favor of hypertonic saline. Besides Marko [39] also published a commentary in 2012, where he thought mounting evidence supported HTS, not mannitol, should be as the better choice for gold-standard therapy for medical management of intracranial hypertension.

Although mannitol remains the osmotic agent most frequently recommended in official guidelines, it is interesting to note that the accumulated clinical evidence is already changing practice.

ADVERSE EFFECTS OF OSMOTHERAPY

There are few studies that focus on the adverse effects of HTS as the primary outcome measure. However, all the studies have reported these as part of their findings.

One of the worst potential complications related osmotherapy is central pontine myelinolysis or osmotic demyelination syndrome, which involves the destruction of myelin primarily within the pons and is clinically evident as lethargy and quadraparesis. The risk is generally associated with rapid correction of hyponatremia with HTS [40].

Osmotherapy may also cause electrolyte disturbances. Mannitol may result in hyponatremia and hypokalemia, followed by hypernatremia, due to its strong osmotic diuretic effect [41]. However, repeated infusion of HTS may increase sodium and chloride concentrations to values far above the normal, resulting in hypernatremia and hyperchloremic acidosis. Additionally, large amounts of potassium may be lost in the urine, resulting in hypokalemia. HTS appears to exert its diuretic effect more from atrial natriuretic peptide (ANP) release than through osmotic effect [31]. In the bolus-dose studies, the mean highest serum sodium concentration was 170.7 mmol/L, but there were no adverse effects though to be related to HTS. Strandvik *et al.* [42] thought it would be prudent that serum sodium level should be measured within 6h of administration if bolus doses are given.

Volume overload is a common side effect of all hyperosmolar solutions and is potentially problematic among patients with cardiopulmonary disease. HTS administration naturally expands in volume, whereas mannitol initially expands, then dehydrates. For patients in whom volume expansion must be maintained, such as those with SAH, HTS provides an elegant solution to both issues of ICP treatment and prophylaxis/treatment of vasospasm. In this population, mannitol is potentially hazardous but can be used with central venous pressure (CVP) monitoring and careful matching of fluid intake and output.

Renal insufficiency or renal failure can not be neglected with osmotherapy. Mannitol, which is excreted unchanged across the glomerular membranes, may cause serious renal failure [43-45]. Though the mechanism is not known, it may be related to high osmolality in tubuli, resulting in acute tubular necrosis. Mannitol has been shown to be an independent risk factor for acute renal failure after severe head injury [46]. As a similar or even higher increase in osmolality from hypertonic saline or urea causes less renal failure [40].

Phlebitis and local tissue damage at the infusion site of hyperosmolar solutions can be caused if infused into the subcutaneous tissues through an infiltrated peripheral vein. Solution of greater than 2% saline must be infused through a central venous catheter [2]. Mannitol also requires the use of an in-line filter to prevent infusion of crystals that may precipitate. But patients with clinical signs of herniation and surgical lesions usually do not delay treatment to obtain central access and usually need short-term hyperosmolar therapy as a bridge to surgical decompression.

Besides, there is a common view that osmotherapy is associated with a rebound phenomenon. This has been tentatively explained by interstitial and intracellular accumulation of the agent in the brain with a reversal the osmotic gradient between the blood and the interstitial and intracellular spaces after withdrawal of the infusion. Knapp *et al.* [3] found that the rebound increase in ICP appears to be smaller with hypertonic saline than with mannitol and that the duration of the reduction in ICP is longer. A meta-analysis comparing hypertonic saline and mannitol supported the existence of a rebound effect from mannitol, but such an effect was not as clear for HTS [37].

CONCLUSION

The management of patients with acutely elevated ICP remains a major challenge. Osmotherapy is a key protocol in numerous treatment, including sedation, controlled ventilation, and decompressive surgery. It safely and effectively lowers acutely raised ICP in a variety of neurological conditions. Although mannitol remains osmotic agent the most frequently used, recent evidence suggests the superiority of hypertonic saline to mannitol.

However, further research into the precise mechanisms of action and into the neurohumoral and immunologic effects is needed. Randomized clinical trials should assess the impact of osmotherapy not only on short-term outcome but also on quality of life in the longer run.

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