Traumatic brain injury (TBI) is one of the leading causes of mortality and disability worldwide. Cerebral oedema is a major cause of raised intracranial pressure (ICP) in patients with TBI and controlling ICP is a major component of TBI management. The extent of initial insult to the brain defines the clinical manifestation following TBI. However, raised ICP and the secondary effects caused by cerebral edema define the severity and outcome of the disease. Mannitol and hypertonic saline (HTS) are widely used to reduce cerebral oedema after TBI. Considerable controversy exists over their choice since studies comparing the ICP-reducing effects of mannitol and HTS have failed to establish the clinical superiority of one over the other.[1-5] HTS has been found to superior in a few animal studies,[6,7] an observation not duplicated in clinical trials.[2,3,5,8-10] Systematic reviews and meta-analyses have also failed to detect any significant differences in mortality or functional outcome in TBI patients treated with HTS and mannitol.[2,8-10] Although two recent meta-analysis[4,11] reported a possible advantage of HTS over mannitol in terms of reduced mortality, ICP reduction and beneficial effects on cerebral perfusion pressure (CPP), current evidence is insufficient to recommend any particular therapy. This review attempts to summarise and consolidate available literature and evidence regarding the controversy on the use of mannitol versus HTS in the treatment of post-traumatic cerebral edema.

Background

Hyperosmolar therapy constitutes the cornerstone of the medical management of cerebral edema.[12-14]

Osmotherapy mainly works on the principle of creating an osmotic gradient in the intravascular compartment of the central nervous system (CNS), thereby using the dominant vectors to draw free water from the intracranial parenchyma into the vascular space [Figure 1]. An ideal hyper-osmolar agent establishes a gradient across the vascular endothelium by staying within the intravascular compartment. To achieve this, it utilises the selective permeability of an intact blood-brain barrier and the reflection coefficient of the agent used. The reflection coefficient is measured on a scale of 0 to 1, with zero being freely permeable and one being impermeable to passive diffusion. The effect of osmotherapy can be measured with serum osmolality. The initial target is an osmolality of 300 to 320 mOsm/L with adjustment as per the clinical circumstances and the ICP requirement. The osmolality can be calculated using the following formula: Osmolality = (2 x sodium) + (glucose ÷ 18) + (blood urea nitrogen ÷ 3). Another important parameter to monitor osmotherapy is the osmolality gap, the difference between measured and calculated osmolality. The two commonly used osmotherapeutic agents are mannitol, which is a sugar alcohol and hypertonic saline (HTS), a salt.

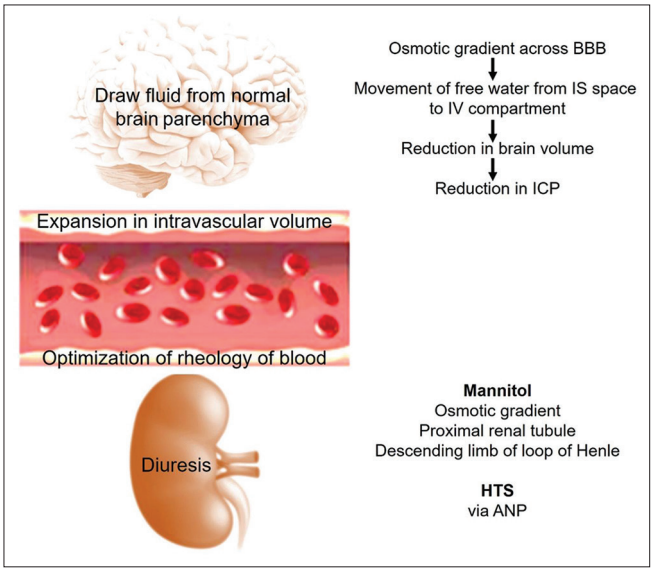

Figure 1: Mechanism of action of hyperosmolar therapy. BBB – blood brain barrier, IS – interstitial, IV – intravascular, HTS – hypertonic saline, ANP – atrial natriuretic peptide

Mannitol

Mannitol, a mannose sugar-derived alcohol, is the traditional gold standard hyperosmolar agent being used in neurosurgical practise for over the last forty years.[15] Mannitol is stable, chemically inert and gets distributed equally within the extracellular compartment. It is not metabolized in the body and is freely filtered by the kidneys without being reabsorbed.[14]

Physiological effects and mechanism of action

Possible mechanism of actions of mannitol includes an immediate plasma expanding action, which further reduces the haematocrit and increases the red blood cell wall flexibility. It is known to shrink RBCs by 15% and thereby reducing the viscosity and increasing the cerebral blood flow and oxygen delivery. This accounts for the marked effects in patients with low cerebral perfusion pressure (CPP) and immediate reduction in ICP after mannitol usage. The late effect occurs once the gradient is established between the plasma and cell. It is the osmotic effect, which occurs after a delay of 15-30 minutes and lasts for over six or more hours. A free radical scavenging mechanism also has been proposed.[14]

An alternative mechanism might be a reduction in cerebral blood volume through vasoconstriction. However, this effect of mannitol also depends on the status of cerebrovascular autoregulation in patients with severe TBI. In patients with preserved autoregulation, infusion of mannitol induces cerebral vasoconstriction. Mannitol, by decreasing blood viscosity, would tend to enhance cerebral blood flow (CBF), but the cerebral vessels would constrict to keep CBF relatively constant, analogous to pressure autoregulation which results in a significant fall in ICP. In patients with absent autoregulation, mannitol increases CBF and the fall in ICP is not significant. A patient with cerebral contusion has a disrupted blood-brain barrier (BBB) around the contusion. Mannitol reduces ICP by drawing fluid from the normal brain parenchyma (not from the contused brain) and thus prevents the herniation syndromes.[16]

Side effects

The eventual diuretic effect of mannitol can be detrimental to a hypotensive patient. It is important that the normovolemic status of the patients should be ensured before giving mannitol. Mannitol can be toxic to renal tubules in the setting of dehydration and is also known to cause metabolic derangements. Each ml of 20% mannitol draws 4 ml of fluid. Adequate maintenance of intravascular volume is a key treatment strategy in patients with neurosurgical problems on mannitol.[1,16]

In the setting of disrupted blood-brain barrier, when mannitol doses are frequently repeated, it is known to create reverse osmotic gradients and causes rebound intracranial hypertension, the so-called paradoxical reverse osmotic gradient. Rebound is seen when large doses of mannitol are administered at a frequency exceeding its urinary excretion rate.[17] Cerebral osmoregulation tries to compensate for these intracerebral osmolar alterations by modifying its content of brain cell "protective" osmoles content, especially the inorganic solutes content, i.e., electrolytes (Na, K, Cl). If the osmolar disturbance is more extensive the brain volume attempts to return to its initial value, by increasing its share of organic "idiogenic" osmoles. These idiogenic osmoles include amino acids, polyols and trimethylamines and the production of idiogenic osmoles results in the attainment of solute equilibrium with cerebrospinal fluid (CSF) causing slow exit and rebound reverse osmotic gradient.

Dosage and guidelines for use

There are few human studies that have validated different regimens of mannitol administration.[15,16] Regarding hyperosmolar therapy, the 3rd Brain Trauma Foundation (BTF) guidelines recommends mannitol at 0.25 gm.kg-1 body weight per dose for controlling raised ICP, while taking care to avoid hypotension (systolic BP <90 mm Hg) (Level 2 evidence). [14] The recommendation was to use mannitol only in patients with trans-tentorial herniation or progressive neurological deterioration not attributable to the extra-cranial causes (Level 3 evidence). As a routine, many neurointensive care units use 20% mannitol as timed boluses of 100-200 ml over 4-6th hourly intervals especially when ICP monitoring is not routinely practiced.[13] Mannitol needs to be stopped when serum osmolality exceeds 320 mOsm/l, or the osmolality gap exceeds >20 mOsm/l.

Hypertonic saline

It was not until the early 1990s that HTS gained prominence as an alternative to mannitol.

Physiological effects and mechanism of action

The response to intravenous infusion of HTS is two-fold and is similar to that of mannitol.[18]

Effect on cerebral blood flow

Initial immediate response (15 to 20 min) of HTS in reducing ICP is due to the optimisation of the rheological properties of blood. It reduces the blood viscosity and haematocrit and changes the physical properties of red blood cells (RBC) like volume, cohesiveness and rigidity. It also reduces the size of the ischemic swollen endothelial cells thereby increasing the diameter of the small capillaries. All these changes cause an improvement in the cerebral blood flow and oxygen delivery, resulting in reflex autoregulatory vasoconstriction of cerebral arterioles that reduces cerebral blood volume and ICP.

Osmotic effects

Osmotic effects occur 15 to 30 minutes after administration of HTS. The permeability of sodium and chloride across the BBB is low and mainly through endothelial cell membrane channels and carriers. Along with it the low reflection coefficient of sodium chloride creates a diffusion vector for fluid in the brain parenchyma to be drawn into the intravascular compartment thereby reducing the intracranial pressure. It has been suggested the osmotic effect happens at the uninjured normal portion of the brain with intact BBB. HTS is a less potent diuretic as compared to mannitol. The diuretic effect is through activation of atrial natriuretic peptide (ANP) rather than direct diuresis like mannitol. The difference and the potential benefits of HTS over mannitol appear after the first 45 min.

Cardiac effects

The initial expansion of intravascular volume to about 2 to 3 times the infused volume sets off a series of cardiovascular responses increasing the cardiac output.

1. Peripheral vasodilation and redistribution of regional blood flow occur due to endothelial smooth muscle relaxation and shrinkage of endothelial cells.
2. Prolonged increase in venous return increases the preload.
3. Decrease in the right and left ventricular afterload by hyperosmotic induced arteriolar vasodilatation enhances the cardiac inotropy.
4. Myocardial function improves with the reduction of myocardial oedema or by increased uptake of calcium with the restoration of transmembrane potential.

Immunomodulatory effects

The immunomodulatory effects are thought to be due to a reduction in endothelial and leukocyte adhesion. There is the attenuation of the neutrophil cytotoxicity and upregulation of the protective effect of lymphocytes. The evidence of immunomodulation with HTS is mainly through animal studies with no clear evidence in human trials.[6,7]

Neurochemical effects

Immediately after the injury, the cerebral microenvironment gets affected by the widespread accumulation of extracellular excitatory amino acids, especially glutamate. This results in widespread neuronal depolarization and accumulation of intracellular calcium increased phospholipase activity and the resultant increase in cell membrane permeability and resulting in cell death. By increasing the extracellular sodium levels hypertonic saline stabilises the resting membrane potential and reduces cell hyperstimulation and cell death.

Side effects

Neurological complications

The potential neurological complications of HTS administration includes central pontine myelinolysis and rebound cerebral edema. Central pontine myelinolysis (CPM) can occur in the setting of rapid raise in serum sodium in the background of chronic hyponatremia, alcohol intoxication and malnutrition. CPM in normonatremic patients is rare and reports are predominantly in animal studies.[19] Rebound cerebral edema is more common with mannitol than hypertonic saline. With an osmotic reflection coefficient of 1.0 and with

poor evidence in literature there is no documented concern of clearly defined rebound cerebral edema with HTS.

Systemic complications

Acute renal failure (ARF) is the most dreaded complication after hypertonic saline infusion although it is infrequent. Severe hypernatremia with sodium levels more than 160 mEq/l directly correlates with ARF. Other than this male gender and pre-existing comorbidities also predict the development of ARF. Hypercholoremic acidosis and hypokalemia are other frequently encountered issues, which can be easily prevented with potassium supplementation. Acute red cell lysis has been observed in animal studies but no human studies have ever reported such a phenomenon. Fluid overload is possible in patients with pre-existing cardiac conditions. HTS is preferably administered using a central line. Infusion phlebitis and local tissue necrosis are possible when long-term infusions are given using peripheral lines. Such a phenomenon is not seen during short-term osmotherapy and while using bolus regimens.

Dosage and guidelines for use

Hypertonic saline is available in various dosing concentrations ranging from 1.9% to 23.4%. Human studies using 7.5% NaCl have shown that the plasma volume increased by 25% and the effect lasted for up to 4 hours with a half-life of 60 min.[18] Most studies show that the ICP remains low for 1- 2 hours.[1,18] There is no evidence to support one concentration over another in control of ICP.

Bolus dosing can be used alone or as an adjunct to infusion therapy. Bolus dosing can be in various formats like volume/dose, ml/kg and mOsm/dose. Current data suggest boluses ranging from 200 to 641 mOsm/dose is safe and effective.[20,21] While using highly concentrated HTS (30 ml of 23.4%), the total osmolar load is kept in the 200-300 mOsm/dose range whereas less concentrated agents (3%, 7.5%) delivers a larger total load at 300 – 900 mOsm/dose.

However, with continuous infusion patients have reached the target serum osmolarity better than with bolus doses. The treatment is titrated based on monitoring serum sodium and serum osmolarity. Current evidence suggests that maintaining hypernatremia and hyperosmolarity is important for the consistent reduction of ICP.[22,23] Serum sodium levels of 145 to 155 meq/l and serum osmolarity <360 mOsml/l provide a predictable and sustained reduction in ICP.[21,22] The osmolality of 3% HTS is similar to that of 20% mannitol. When given as intermittent bolus the dose in ml of 20% mannitol and 3% saline is the same.[20,21] When given as continuous infusion the dose of 3% HTS ranges from 0.1 ml/kg to 1 ml/kg titrated to ICP values or serum sodium values. HTS needs to be stopped when serum sodium exceeds 155 mEq/l or when serum osmolality exceeds 360 mOsm/l.

Summarizing, an ideal way of initiation of HTS treatment is to start with an initial bolus of 30 ml of 23.4% HTS to achieve a target serum sodium of 145 – 155 and maintain the sodium levels by titrating the infusion of 3% HTS in the range of 0.1 – 2.5 ml/kg/hour. This can be supplemented with daily monitoring of serum sodium, serum osmolarity and hourly urine output.[11]

Paediatric TBI

HTS is gaining popularity in the management of severe TBI in children. Although mannitol is commonly used in the management of raised ICP in pediatric TBI, no studies meeting inclusion criteria were identified for use as evidence for this topic in the 3rd BTF guidelines (2019) for the management of paediatric severe TBI.[23] In these guidelines, there was insufficient evidence to support a level I recommendation for hyperosmolar therapy. These guidelines gave level II recommendation for use of bolus of HTS (3%) in children with intracranial hypertension. The recommended effective doses for acute use are between 2 and 5 mL/kg over 10–20 minutes. There was a level III recommendation for continuous infusion HTS is in children with intracranial hypertension. The suggested effective doses as a continuous infusion of 3% saline were between 0.1 and 1.0 mL/kg of body weight per hour, administered on a sliding scale. The guidelines suggest that the minimum dose needed to maintain ICP < 20 mm Hg should be used. They also suggested 0.5 mL/kg with a maximum of 30 mL bolus of 23.4% HTS for refractory ICP. The guidelines also gave safety recommendations. In the context of multiple ICP-related

therapies, avoiding sustained (>72 hr) serum sodium greater than 170 mEq/L was suggested to avoid complications of thrombocytopenia and anemia, whereas avoiding sustained serum sodium greater than 160 mEq/L was suggested to avoid the complication of deep vein thrombosis (DVT).

Choosing sugar or salt

An ideal osmotherapeutic agent should be inert, non-toxic, have low systemic side effects, should increase the serum osmolality to the desired range and thereby reduce cerebral oedema and raised intracranial pressure. An increase in cerebral perfusion pressure and brain tissue oxygen partial pressure (pBtO2) are indirect effects that facilitate recovery and favourable outcome.[14] Multiple studies have attempted to compare mannitol and HTS and several meta-analysis and systematic reviews have attempted to compile the observations from these studies.[2,22,24-26]

A comprehensive comparison of multiple variables which included mortality, a favorable outcome, ICP, cerebral perfusion pressure (CPP), brain tissue oxygen partial pressure (pBtO2), treatment failures, duration of elevated ICP per day and side effects have been published in a recent meta-analysis by Schwimmbeck *et al*.[4] They did not observe any significant difference in mortality and favourable outcome rates between the two treatments. At 30 to 60 minutes after treatment, there was no significant difference in ICP between HTS and mannitol whereas HTS therapy significantly lowered ICP compared with mannitol at 90 to 120 minutes. CPP was higher between 30 and 60 minutes after treatment with HTS compared with mannitol and even more so between 90 and 120 minutes after treatment. Possibly, the greater effect of HTS on CPP is related to its superior hemodynamic profile, in contrast, mannitol is a diuretic and can therefore, cause hemodynamic instability. The larger differences between ICP and CPP in the second hour after treatment might be related to the longer duration of action of HTS. Brain tissue oxygen partial pressure (pBtO2) remained the same in the two groups.

A number of adverse effects of mannitol have been identified, such as acute renal failure, rebound ICP elevation, and hypovolemia.[11] A non-significant increase in the incidence of pneumonia was noticed in the HS group but there was a tendency toward superiority of HTS in terms of treatment failure.

In another recent comprehensive meta-analysis wherein a total of 125 patients from four randomized trials were included, the authors reported no significant differences between the two groups in the outcome, mortality or side effects.

The results of recent meta-analyses do not lead to a specific recommendation to select HTS or mannitol as a first-line for patients with elevated ICP caused by TBI. [2,22,24,25,26] However, for refractory raised ICP, HTS seems to be preferred. HTS is also preferred in hypovolemic states. The contraindications to the use of HTS are platelet count less than 100×10^9/L or abnormal clotting with INR greater than 1.4 or a rise in creatinine more than twice the baseline value. A bolus dose of mannitol may be considered as an alternative to HTS in this setting [Figure 2].

The recent 4th BTF guidelines (2016) do not recommend any specific hyperosmolar agent in severely head-injured patients due to a lack of quality evidence on clinical outcomes. They had to carry forward the 3rd BTF guideline statement though without supporting it. However, the guidelines for the management of TBI in children recommend the use of HTS.[26]

In spite of gaining popularity, HTS is still not preferred by many neurosurgeons in India.[27] The perceived barriers to the use of HTS are the absence of strong evidence clinical guidelines approving its use, and the easy availability of a comparable treatment (mannitol). Despite an ever-growing body of evidence showing promising results with the use of HTS to manage increased ICP in adult patients with severe TBI, there have been no recommendations regarding the superiority of one over the other.

Our protocol

At our institute, we follow the following steps in the management of raised ICP for TBI when an EVD is inserted for ICP monitoring [Figure 3]. When an EVD is not inserted or cannot be inserted, the management of patients with TBI is with frequent clinical and CT

scan monitoring. If there are clinical or CT indicators of raised ICP like low GCS score, midline shift, cerebral oedema, effacement of basal cisterns or obliteration of the third ventricle then hyperosmolar therapy is given.[13] We prefer to use mannitol 20% as the first agent at a dose ranging from 100 ml three times a day to 150 ml four times a day depending on the severity of ICP on the basis of CT scan findings. The initial measures include head-end elevation, sedation, analgesia with ventilation depending on the severity of the injury. ICP monitoring is employed as per BTF guidelines. Hyperosmolar therapy is ideally used as the fourth step in the management of raised ICP after cerebrospinal fluid drainage through external ventricular drainage (EVD.

The choice of hyperosmolar therapy is dependent on the differences between mannitol and HTS as given in Table 1. We have not found any difference in the reduction of ICP

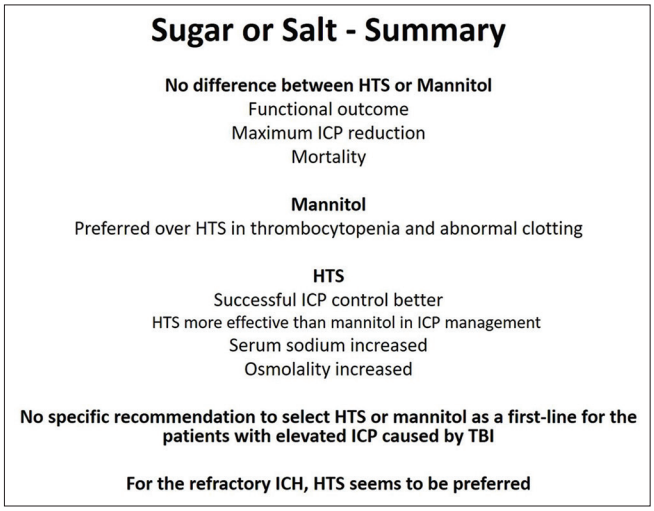

Figure 2: Summary of hyperosmolar therapy. HTS – hypertonic saline, TBI – traumatic brain injury, ICH – intracranial hypertension

Table 1: Differences between mannitol and hypertonic saline

	Mannitol	Hypertonic Saline
Mechanism of action	Free radical scavenger	Resting membrane potential restoration
		Cell volume restoration
		Immunomodulation
Relative coefficient	0.9	1.0
Maximum permissible serum osmolarity	320 mOsm/L	360 mOsm/L
Diuretic effect	More (Direct osmotic)	Less (Indirect via ANP)
Hemodynamic effect	Compromise intravascular volume	Augment intravascular volume
	Hypovolemia	Maintains CVP
	Hypotension	Maintains MAP and CO
Half life	2-4 hours	Unknown
Adverse effects	Hypotension	Cardiac failure
	Hyperkalemia	Hypokalemia
	Renal failure	Coagulopathy
Dosing	Bolus	Continuous with bolus
	Effectiveness decreases with repeated administration	More prolonged effect
BTF Recommendation for Pediatric TBI	Not mentioned	Level II for bolus
		Level III for continuous infusion

CVP - Central venous pressure, MAP - Mean arterial blood pressure, CO - Cardiac output, ANP - Atrial natriureteric peptide, BTF - Brain trauma foundation, TBI - Traumatic brain injury

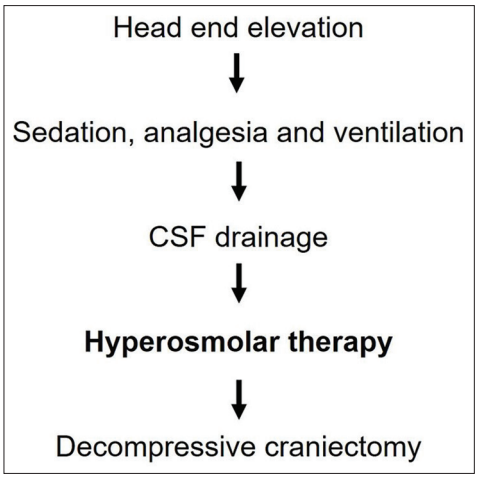

Figure 3: Proposed stepwise management of raised intracranial pressure

or the outcome with the use of either hyperosmolar agent.[20,21] HTS is given more often to children as compared to adults. HTS is also resorted to when there is no response to mannitol. The dose used for 20% mannitol and 3% hypertonic saline is the same. In patients with severe cerebral edema we prefer to administer HTS as a continuous infusion.

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