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# Use of Hypertonic Saline in Neuroanesthesia and Neurocritical Care Practice: A Narrative Review

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## Abstract

Hypertonic saline (HTS) is a group of fluids containing sodium and chloride in a higher concentration as compared to physiological saline. The authors have conducted this review to evaluate the use of HTS in neuroanesthesia and neurocritical care. The articles for this narrative review on HTS were searched on databases like PubMed Central, EMBASE, and Google Scholar using the Medical Subject Headings keywords "Hypertonic Saline," "Neuroanesthesia," and "Neurocritical Care." The review focuses on the mechanisms of HTS and its in routine clinical practice. The results of various comparative studies between HTS and mannitol and guidelines regarding the use of HTS have also been reviewed. HTS can be used to treat hyponatremia, reduce intracranial pressure, provide intraoperative relaxed brain, and aid in resuscitation during cardiogenic, neurogenic, and septic shock. Its side effects include renal toxicity in the case of hypernatremia, rebound intracranial hypertension, volume overload, dyselectrolytemia, phlebitis, local tissue damage, and osmotic demyelination syndrome in the case of rapid correction of serum sodium concentration.

**Keywords**
- hypertonic saline
- neuroanesthesia
- neurocritical care

## Introduction

Tonicity is the ability of an extracellular solution to make water move into or out of a cell by osmosis. A solution is considered hypertonic if its solute concentration is higher than the cell and the solutes cannot cross the membrane. Hypertonic saline (HTS) is a group of fluids containing sodium and chloride in a higher concentration as compared to physiological saline (0.9% w/v).[1] The use of HTS for the reduction of the brain bulge was published by Weed and McKibben in 1919.[2] Since then, there has been a myriad of studies using HTS in various medical and surgical conditions. The drug has proven its mettle in operation theatres, intensive care units (ICUs), and the emergency department. Numerous studies have shown that HTS is as effective as its competitor drug, mannitol. Despite proving its mettle in multiple clinical trials in varied settings time and again, HTS could not earn its place in routine clinical practice. Hence, we conducted this review to condense the vast information from the existing literature to highlight its benefits, application, side effects, and to draw a consensus regarding its clinical use.

## Methodology

The pertinent articles for this narrative review were searched on databases like PubMed Central, EMBASE, and Google Scholar. The Medical Subject Headings keywords used were "Hypertonic Saline," "Neuroanesthesia," and "Neurocritical Care." The articles were thoroughly analyzed by the authors before the final drafting of this article.

## Pharmacology

HTS is used clinically in various concentrations ranging from 1.8 to 30% (►**Table 1**).[3] Only 3 and 5% of HTS are currently approved by the Food and Drug Administration for use in

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patients with hyponatremia and increased intracranial pressure (ICP). To achieve volume expansion, dextrans have been added to it in a few formulations.

## Mechanism of Action

There are various mechanisms through which HTS decreases the ICP, maintains the cerebral perfusion pressure (CPP), decreases neuronal toxicity, and finally prevents secondary injury (►**Fig. 1**). The various effects and the underlying mechanisms are as follows.

1. Osmotic effect:

The mechanism of action of HTS is predominantly through the marked osmotic shift of fluid. Intravenous injection of HTS causes an increase in plasma osmolality and oncotic pressure, which shifts the water from the intracellular to the interstitial and intravascular space.[4] The reflection coefficient of the cell membrane for sodium is about 10 times more than that of the endothelial membrane (1 vs. 0.1), which implies that most of the fluid shift occurs from the intracellular space.[3] So, the HTS reduces the osmotic gap, cerebrospinal fluid production, and ICP, hence it improves intracranial compliance.[5]

2. Microcirculatory and vascular effects:

HTS normalizes the endothelial cell volume, which increases because of endothelial cell membrane ion exchange dysfunction. It increases the capillary diameter and reduces the resistance to blood flow.[6,7] The above mechanisms improve microcirculation and counteract vasospasm and hypoperfusion by increasing cerebral blood flow (CBF).

**Table 1** Sodium concentrations and osmolarity of various concentrations of the hypertonic saline

| Solution | Sodium concentration (mmol/L) | Osmolarity (mOsm/L) | Equiosmolar dose (275 mOsm) |
|---|---|---|---|
| NaCl 0.9% | 154 | 308 | 892 |
| Ringer's lactate | 130 | 275 | 1000 |
| Saline 1.7% | 291 | 582 | 472 |
| Saline 3% | 513 | 1027 | 268 |
| Saline 5% | 856 | 1711 | 161 |
| Saline 7.2%/ HES 6% (200/0.6) | 1232 | 2464 | 112 |
| Saline 7.5% | 1283 | 2566 | 107 |
| Saline 7.5%/ Dextran 70 6% | 1283 | 2568 | 107 |
| Saline 10% | 1712 | 3424 | 80 |
| Saline 23% | 4004 | 8008 | 34 |
| Saline 30% | 5000 | 10,000 | 27.5 |

Abbreviation: HES, hydroxyethyl starch.

The effect on urine output and sodium excretion is an interplay between many mechanisms of action. The increased intravascular volume and blood pressure lead to increased renal perfusion pressure, glomerular filtration rate, and decreased sodium reabsorption. Hyperosmolarity causes the release of antidiuretic hormone, but this is counteracted due to vagal stimulation and atrial natriuretic peptide release, finally leading to moderate diuresis and natriuresis.[8]

3. Effect on hemodynamics:

The intravenous infusion of HTS leads to osmotic shifts, increasing the intravascular volume, mean arterial pressure (MAP), stroke volume, and cardiac output. Also, the volume required for plasma expansion with HTS is less than that of normal saline.[9] The increase in MAP after a bolus of HTS lasts for 15 to 75 minutes but can be further extended by adding colloids.[10] HTS decreases the myocyte edema and causes the increased uptake of calcium, hence improving the myocardial activity.[11,12]

4. Immunologic effect:

HTS-dextran prevents traumatic brain injury (TBI)-induced upregulation of leucocyte adhesion molecules, decreases the levels of tumor necrosis factor-α (TNF-α) and interleukin (IL)-10, and also improves the balance between coagulation and fibrinolysis.[13] It is also found that HTS has a role in decreasing cerebral edema by inhibiting microglia-derived TNF-α and IL-1β-induced upregulation of $Na^+$-$K^+$-$Cl^-$ cotransporter.[14]

5. Neurochemical effect:

HTS increases the extracellular $Na^+$ concentrations which return the $Na^+$-glutamate cotransporter to its normal function. This mechanism helps in reducing the glutamate release and thus, prvents secondary brain injuries. The intracellular concentration of ions like $Na^+$, $Cl^-$, and $Ca^{+2}$ are restored. All the above mechanisms lead to a reduction in neuronal excitation.[15]

## Clinical Uses of Hypertonic Saline

HTS can be used in different clinical situations (►**Fig. 2**), like reduction of raised ICP, in routine brain surgery, and shock.

1. *Intracranial pressure reduction*:

HTS can be used to reduce raised ICP in patients with TBI, subarachnoid hemorrhage (SAH), stroke, and mixed brain injury.

(a) *Traumatic brain injury*:

*Adult patients*:

Among the available concentrations, 3 and 7.5% HTS are the most used in TBI patients. Huang et al studied the effect of a rapid infusion of 300 ml of 3% HTS over 20 minutes on ICP in severe TBI patients and found a decrease in ICP at 20 and 60 minutes.[16] Qureshi et al performed a retrospective review and concluded that prolonged infusion of HTS does not

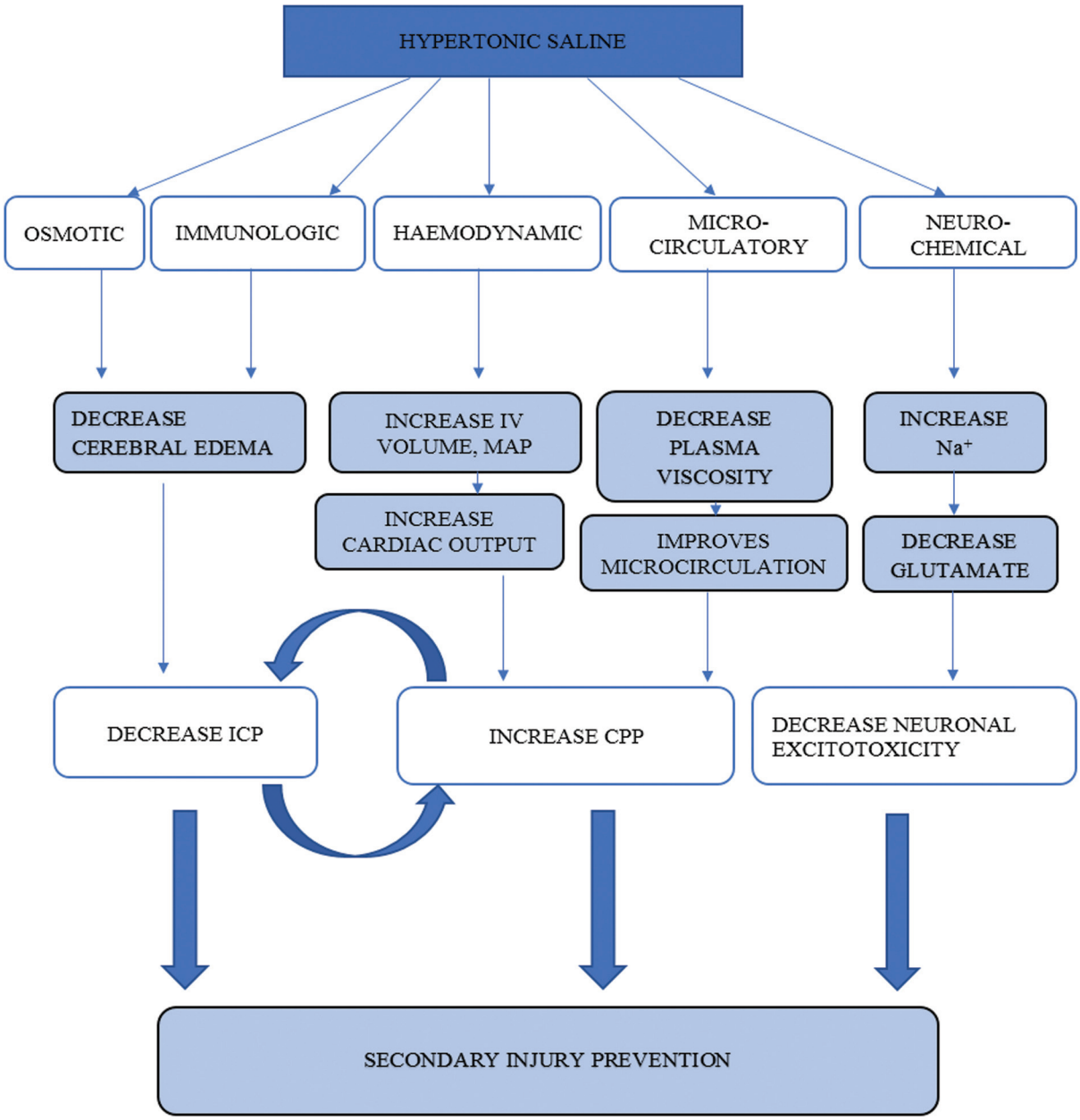


**Fig. 1** Various mechanisms of action of hypertonic saline.

decrease the requirement for other interventions and serves no difference in in-hospital mortality.[17] The effects of 7.2% HTS on ICP, serum sodium, osmolality, cerebral, and systemic hemodynamics were studied in moderate to severe TBI patients, and found that it reduces ICP without changing the CBF.[18] Note that 7.5% HTS was found to decrease the number of intracranial hypertension episodes and rate of clinical failure compared to 20% mannitol.[19] However, when used in prehospital settings for the resuscitation of TBI patients, 7.5% HTS showed no differences in mortality or neurological outcome compared to the Ringer's lactate solution.[20] Marked reduction in cerebral water content was seen one hour after the infusion of 18% HTS among patients with refractory intracranial hypertension following TBI.[21] A retrospective study was done to compare 23.4% HTS and 20% mannitol among patients with raised ICP. It was found that the ICP reduction was similar in both groups but the mean duration of the ICP reduction by HTS was longer than mannitol (96 vs. 59 minutes).[22] Berger-Pelleiter et al performed a meta-analysis and opined that HTS cannot be recommended as a first-line hyperosmolar agent, and it does not decrease ICP and has no mortality benefits.[23] However, a meta-analysis by Han et al concluded that compared to mannitol, HTS had better ICP and CPP control at 30 to 60 minutes and lower treatment failure. There was no significant effect on the outcome.[24] Similarly, another meta-analysis by Shi et al concluded that HTS had a more sustained effect on ICP and CPP compared to mannitol.[25] ►**Table 2** summarizes the various studies

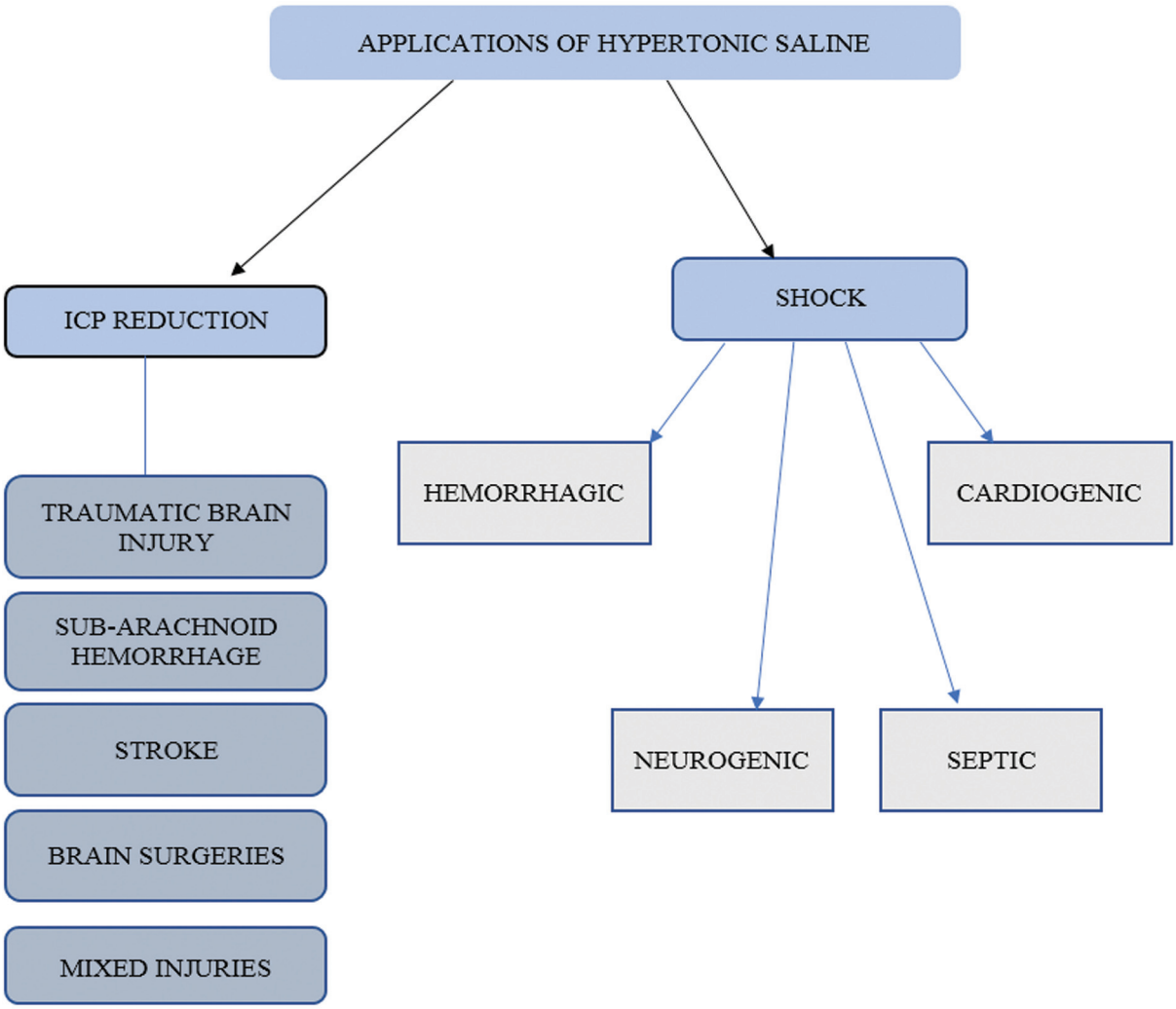


**Fig. 2** Uses of hypertonic saline.

comparing HTS and mannitol as an osmotherapy in TBI patients.[26–31]

*Pediatric patients*:

As per the pediatric head injury guidelines, 3% HTS can be used as an osmotherapy in patients with intracranial hypertension with effective doses between 2 and 5 mL/kg over 10 to 20 minutes (level II) or as a continuous infusion of 0.1 to 1 mL/kg/hour to maintain ICP less than 20 mm Hg (level III).[32] Infusion of 20% HTS was also found to decrease ICP in pediatric TBI patients.[33,34] Kochanek et al compared the ICP measurements between 3% HTS and mannitol in pediatric patients with severe TBI and found that the HTS group had greater reductions in ICP along with an increase in CPP.[35]

Brain Trauma Foundation (BTF) guidelines suggest the use of hyperosmolar therapy to reduce ICP but not to improve neurological outcome. However, they also do not recommend any one agent over the other. Neurocritical Care Society (NCS) favored the use of HTS over mannitol for the initial management of decreasing ICP and cerebral edema in patients with TBI. They suggested that neither HTS nor mannitol has a role in improving the neurological outcome of patients with TBI. Also, they recommended against the use of HTS in the prehospital setting to improve neurological outcomes.[36]

(b) *Subarachnoid hemorrhage*:

HTS can be used in SAH patients to decrease ICP and maintain CPP, CBF, and brain tissue oxygenation (PbtO2). Bentsen et al used a 2mL/kg bolus of 7.2% HTS in 6% hydroxyethyl starch (HES) during the episodes of raised ICP > 20 mm Hg in seven patients with SAH and found a decrease in ICP (58%) and an increase in CPP (26%) at 40 minutes. The effects lasted for 3 hours with no rebound hypertension.[37] However, when 7.2% saline in 6% HES was given in patients with SAH having ICP 10 to 20 mm Hg, a mean decrease in ICP of 3.3 mm Hg (7.2%) was noted. The CPP increase was also greater in the HTS group (5.6 vs. 0.2 mm Hg).[38] Tseng et al infused a 2-mL/kg bolus of 23.5% HTS in patients with SAH and found that CPP increased by 26.8% and ICP decreased by 74.7% at 1 hour. It was associated with a decrease in cerebrovascular resistance and increased CBF in ischemic regions of the brain by 20 to 50%.[39] Al-Rawi et al used an infusion of 23.5% HTS among 14 SAH patients and found a significant increase in CPP, CBF and PbtO2, with a

**Table 2** Summary of the various studies comparing HTS and mannitol (M) for osmotherapy in traumatic brain injury (TBI) patients

| Study | Type of study | No. of patients (episodes) | Included patients | Osmotherapy | Results |
|---|---|---|---|---|---|
| Han et al[24] | Meta-analysis | 1,392 | TBI with elevated ICP | HTS<br>M | -HTS lowers ICP, increased CPP, and had lower treatment failure rate<br>-No effect on outcome |
| Shi et al[25] | Meta-analysis | 544 | Severe TBI with elevated ICP | 3% HTS<br>20% M | -HTS and M both reduce ICP<br>-HTS: sustained effect on ICP |
| Cottenceau et al[26] | RCT | 47 (165) | Severe TBIwith ICP $>$ 15 mm Hg | 7.5% HTS<br>20% M | -HTS and M both reduced ICP and increased CPP |
| Huang et al[27] | RCT | 33 (238) | Severe TBIwith ICP $>$ 20 mm Hg for more than 5 min | 15% HTS<br>20% M | -The maximum ICP reduction, action onset, and duration of action was similar in HTS and M |
| Ichai et al[28] | RCT | 34 (69) | Severe TBI with ICP $>$ 25 mm Hg for more than 5 min | HSL(hypertonic saline lactate)<br>20% M | -HSL was superior in reducing ICP with better neurological outcome in HSL group |
| Jagannatha et al[29] | RCT | 38 (488) | Severe TBI with ICP $>$ 20 mm Hg for more than 10 min | 3% HTS<br>20% M | -HTS: shorter duration of increased ICP and inotrope requirement |
| Mangat et al[30] | Retrospective cohort | 50 | Severe TBI | 3% HTS20% M | -HTS is better than M in reducing ICP with shorter ICU stay and no effect on Clinical outcome |
| Sakellaridis et al[31] | RCT | 29 (199) | Severe TBI with ICP $>$ 20 mm Hg for more than 5 min | 15% HTS<br>20% M | -Similar ICP reduction and duration of action |

Abbreviations: CPP, cerebral perfusion pressure; HSL, hypertonic saline lactate; HTS, hypertonic saline; ICP, intracranial pressure; ICU, intensive care unit; RCT, randomized controlled trial.

significant decrease in ICP and the lactate-pyruvate ratio at 60 minutes.[40] NCS gave a conditional recommendation to use a symptom-based bolus dose of HTS over the conventional sodium level targeted dosing for decreasing the ICP/cerebral edema in patients with SAH (very low-quality evidence).[36] ►**Table 3** summarizes the various studies comparing HTS and mannitol for osmotherapy in SAH patients.[39–41]

(c) *Stroke*:

HTS has been used in stroke patients with varying results. Schwarz et al used 75 mL of 10% HTS in patients with stroke having raised ICP not responding to the conventional therapy. They found that HTS was effective in decreasing the ICP and increasing the CPP.[42] A systematic review by Chugh et al on the effects of continuous HTS therapy in patients with acute ischemic infarcts, concluded that although HTS administration demonstrated improvement in the ICP, there was no significant improvement in the mortality and neurological/functional outcomes.[43]

NCS does not favor HTS or mannitol over each other to improve neurological outcomes in patients with acute ischemic stroke. They suggested the use of either agent to decrease ICP and cerebral edema in patients with acute ischemic stroke. In patients with ICH, they suggested symptom-based dosing or sodium-targeted infusion of HTS to manage raised ICP and cerebral edema.[36]

(d) *Mixed injuries*:

Harutjunyan et al concluded that 2% HTS-HES decreases ICP for a longer duration compared to 15% mannitol in patients with raised ICP due to mixed cerebral pathologies (TBI, SAH, ICH, or brain tumor).[44] Seventy-six events of transtentorial herniation (TTH) in patients with mixed cerebral pathologies were managed with 23.4% NaCl along with conventional therapy. Clinical reversal of TTH occurred in 75% of the events.[45] So, HTS use in mixed cerebral pathologies can be beneficial.

2. *Brain surgery*:

The use of HTS during routine craniotomy can achieve a better brain relaxation score (BRS) with stable hemodynamics compared to 20% mannitol. Toung et al demonstrated that the continuous intravenous infusion of 7.5% HTS for 48 hours improves cerebral edema in affected and noninjured cerebral hemispheres compared to mannitol or furosemide.[46] Hernández-Palazón et al studied the dose–response relationship between 3 and 5 mL/kg of 3% HTS on intraoperative BRS. They found a similar effect on BRS and postoperative outcomes.[47] Rozet et al compared 7.5% HTS and 20% mannitol and found

**Table 3** Summary of the various studies comparing HTS and mannitol (M) for osmotherapy in subarachnoid hemorrhage (SAH) patients

| Study | Type of study | No. of patients (episodes) | Included patients | Osmotherapy | Results |
|---|---|---|---|---|---|
| Tseng et al[39] | Clinical trial | 10 (17) | Poor grade SAH | 23.4% HTS | HTS infusion increases regional CBF and CPP for 3 h |
| Al-Rawi et al[40] | Clinical trial | 14 | Poor grade SAH | 23.5% HTS | HTS improves the CBF, tissue oxygenation, and metabolism |
| Al-Rawi et al[41] | Comparative study | 44 | Poor grade SAH | 23.5% HTS | HTS increases ABP, CPP, oxygenation, increases flow velocity > 240 min, and decreases ICP > 300 min |

Abbreviations: ABP, arterial blood pressure; CBF, cerebral blood flow; CPP, cerebral perfusion pressure; HTS, hypertonic saline; ICP, intracranial pressure.

BRS to be comparable between both the groups with stable hemodynamics in the HTS group.[48] So, HTS can be used as an alternative hyperosmolar agent to achieve desirable BRS in routine supratentorial surgeries. ►**Table 4** summarizes the various studies comparing HTS and mannitol for decreasing the intraoperative brain bulk in patients undergoing brain surgery.[49–52]

3. *Shock*:

HTS can be useful in the management of different types of shock like hypovolemic, cardiogenic, neurogenic, and septic.

I. Hypovolemic shock:

Fluid resuscitation with HTS in trauma patients restores blood volume, regains tissue perfusion, and reduces mortality.[53] Single boluses of 7.5% HTS in combination with dextran in posttrauma patients was found to increase the blood pressure successfully but sustained increase in the blood pressure beyond one hour was found in only one study.[54–56]

II. Cardiogenic shock:

The infusion of HTS/HES increases left ventricular preload and reduces left ventricular afterload and hence leading to improvement of left ventricular systolic function.[57] A study by Gayatri et al compared the effect of a single bolus of 20% mannitol (5 mL/kg) or 3% HTS (5 mL/kg) on global myocardial function using a tissue Doppler-derived myocardial performance index in 50 adult patients undergoing elective supratentorial craniotomy and found no significant differences in myocardial performance and left ventricular filling pressure.[58] It was seen in animal studies that HTS increases cardiac performance by increasing $Na^+$ concentration in the paraventricular nucleus and cerebral angiotensin receptor (AT-1) induced a positive inotropic effect.[59] Licata et al proposed HTS as a treatment for refractory heart failure along with high-dose diuretic therapy.[60] Zampieri and Caruso demonstrated the successful use of HTS as primary therapy for treatment in a 90-year patient with heart failure. The use of 100 mL of 10% HTS led to hemodynamic stabilization and improvement in the breathing pattern of the patient within 3 minutes.[61]

III. Neurogenic shock:

HTS bolus during spinal anesthesia (iatrogenic neurogenic shock) increases blood pressure, and reduces the requirement for fluids and vasopressors.[62] Nout et al documented that the repeated injections of 5% HTS attenuated spinal cord swelling and edema as evidenced by magnetic resonance imaging in experimental spinal cord injury in animal models.[63] The HTS can be useful in neurogenic shock.

**Table 4** Summary of the various studies comparing HTS and mannitol for decreasing the intraoperative brain-bulk in patients undergoing brain surgery

| Study | Type of study | Osmotherapy | Results |
|---|---|---|---|
| Singla et al[49] | RCT | 3% HTS<br>20% M | Brain relaxation score was same in both but better hemodynamic stability in HTS group |
| Barik et al[50] | RCT | 20% M<br>3% HTS<br>8.4% $NaHCO_3$ | Better brain relaxation with 8.4% $NaHCO_3$ than HTS and mannitol |
| Ali et al[51] | Randomized, double blind study | 3% HTS<br>20% M | Better ICP reduction with HTS |
| Sokhal et al[52] | RCT | 3% HTS<br>20% M | Comparable brain relaxation with HTS and M but better hemodynamic control with HTS |

Abbreviations: HTS, hypertonic saline; ICP, intracranial pressure; RCT, randomized controlled trial.

IV. Septic shock:

The use of 7.5% HTS/Dextran 70 was associated with short-lived improvement in hemodynamic status in patients with severe sepsis compared to normal saline.[64] It can also improve the oxygen delivery and cardiac output in septic shock patients.[65] Effat et al used HTS in forty critically ill patients with septic shock, where it decreases CRP levels, improves in cardiac functions, sepsis scores, use of vasopressors, decreases ICU stay, and mechanical ventilation days.[66] So, the use of HTS can be beneficial in septic shock patients.

## Complications

The use of HTS can be associated with the following complications:

(1) *Renal complications*:

The upper safe limit of serum osmolarity is 365 mOsm/L with HTS in patients with TBI.[63] HTS resuscitation was associated with a fourfold increase in acute renal failure (ARF) and a twofold increase in mortality.[67] Hypernatremia is a risk factor for the development of ARF after SAH.[68] However, a mean serum sodium concentration of $160 \pm 10$ mEq/L and the highest serum sodium concentration of 182 mEq/L was not associated with the development of renal failure. Although, a positive correlation was seen between serum Na and creatinine levels.[69]

92) *Rebound intracranial hypertension*:

Although the phenomenon of rebound intracranial hypertension (RIH) is more common with the use of mannitol, continuous osmotherapy with HTS poses a risk of RIH. Prolonged hyperosmolar therapy causes the equilibration of the osmotic gradient across the blood–brain barrier (BBB). After the setting of a new balance, when the hyperosmolar the agent is stopped, water moves back into the brain following the reverse gradient.[70–73] There is also the formation of "idiogenic osmoles" within the brain cells, which increase the osmotic activity and result in water retention or leaky BBB.

(3) *Osmotic demyelination syndrome*:

The rapid increases in serum sodium concentrations can lead to the occurrence of osmotic demyelination syndrome, especially in chronic hyponatremic patients. However, the patients with TBI who were given HTS failed to show any evidence of central pontine myelinolysis in imaging or postmortem studies.[74]

(4) *Systemic side-effects*:

*Volume overload*: The effect of HTS on volume expansion can act as a double-edged sword as along with increasing blood pressure, it may lead to chronic heart failure in patients with preexisting cardiopulmonary or renal dysfunction.[75]

*Electrolyte imbalance*: After the HTS administration, urinary loss can cause hypokalemia.[76] The high chloride load from HTS also causes hyperchloremic metabolic acidosis.[55]

(5) *Others*:

Large-volume infusions of HTS are associated with coagulation dysfunction when more than 7.5% of blood volume is replaced.[77] It is due to decreased platelet aggregation, prolonged prothrombin time, and prolonged activated partial thromboplastin time. Phlebitis and local tissue damage can occur when HTS is administered through a peripheral line. HTS can increase the risk of infections due to its immunomodulatory effect.

## Conclusion

HTS is an important hyperosmolar agent in the neuroanesthesiologists' armamentarium. It can be a potential alternative to mannitol, because of its multipronged mechanism of action and multidimensional use. The BTF recommends the use of HTS over mannitol in pediatric patients; however, in adult patients there is no agent that has been proven to be superior to the other. It can be used for controlling the ICP in patients with SAH and stroke as an alternative to mannitol. However, the mortality benefit and the effect on the outcome are quite dubious. HTS is also effective for intraoperative ICP reduction during routine brain surgeries. It also offers the benefit of maintenance of intravascular volume, especially in patients with compromised cardiac function and polytrauma. Although not well-established, HTS may play a role in hemodynamic stabilization in patients with septic and cardiogenic shock. However, its use should be well-surveilled to watch for its side effects.

Conflict of Interest
None declared.

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