Hyperosmolar Fluids

Cristiane Tavares,
Ana Laura Lindner Latorre de Alcântara,
Kazuco Nakai Murata, and Seigi Sasaki

Abstract

Intravenous hyperosmolar fluids have been used for the clinical management of intracranial hypertension. The most suitable agent depends on the patient's age, comorbidities, and clinical status. Since hypertonic saline causes an intravascular volume expansion, it can be advantageous for hypovolemic patients. Still, it should be used with caution in patients with cardiac heart failure, in whom it may precipitate acute pulmonary edema. In contrast, mannitol induces a strong diuretic response that can lead to a severe blood volume depletion that should be promptly treated to avoid complications. Other concerns related to its use are the rebound phenomenon and a potential risk of hematoma expansion in patients with intracranial hemorrhages. The main concern in patients receiving hypertonic saline is hypernatremia. It poses a theoretical risk of osmotic demyelination when serum sodium levels rise quickly, especially in hyponatremic patients. Both agents can cause renal injuries but through distinct mechanisms. Whereas high serum mannitol concentrations can lead to osmotic nephrosis, renal function impairment associated with hypertonic saline infusion seems to be mediated by hypernatremia and hyperchloremia. Further research is warranted to determine the optimal agent and their best means of administration (boluses vs. continuous infusions) for each neurocritical condition. More extensive clinical trials are needed to address long-term outcomes, adverse events, and quality of life with both agents.

Keywords

Hypertonic solutions · Mannitol · Hypertonic solution · Saline · Intracranial hypertension · Traumatic brain injuries · Brain edema · Anesthesia · Neurosurgery

C. Tavares (✉)
Department of Anesthesiology, Surgical Sciences and Perioperative Medicine, Hospital das Clinicas, University of Sao Paulo Medical School, Sao Paulo, Brazil
e-mail: cristiane.tavares@hc.fm.usp.br

A. L. L. Latorre de Alcântara
State Institute of Brain Paulo Niemeyer, Rio de Janeiro, Brazil

K. N. Murata
Department of Functional Neurosurgery, Hospital das Clinicas, University of Sao Paulo Medical School, Sao Paulo, Brazil
e-mail: kazuco.murata@hc.fm.usp.br

S. Sasaki
Portuguese Beneficence Hospital, Sao Paulo, Brazil
e-mail: seigi@ig.com.br

Hyperosmolar Fluids

As early as 1919, Weed and McKibben observed noticeable changes in the brain volume after the infusion of hypertonic or hypotonic solutions, disrupting the long-held dogma that the volume

H. Prabhakar et al. (eds.), *Transfusion Practice in Clinical Neurosciences*,
https://doi.org/10.1007/978-981-19-0954-2_5

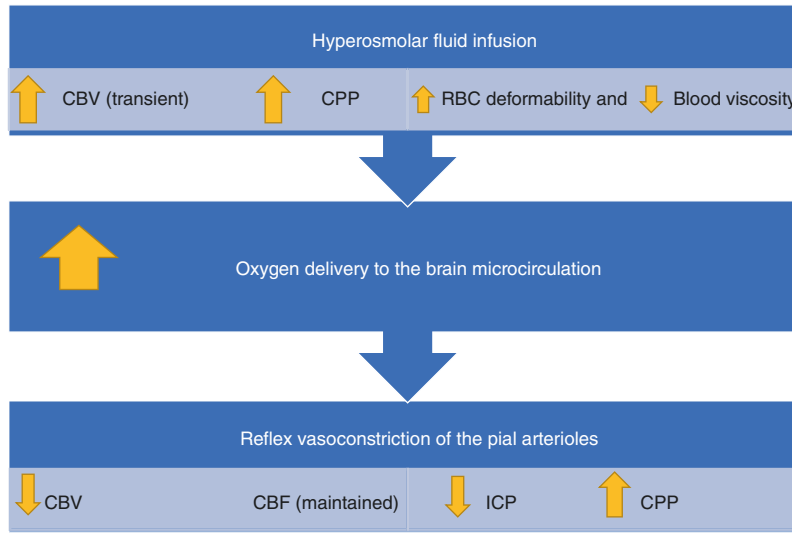

Fig. 1 Hyperosmolar fluid mechanism of action (based in Freeman and Welbourne [4]). (CBV, cerebral blood volume; CPP, cerebral perfusion pressure; RBC, red blood cell; CBF, cerebral blood flow; ICP, intracranial pressure)

of the brain was constant [1]. The first case series in which hypertonic fluids (initially in the form of urea) were used to treat elevated intracranial pressure were described in the 1950s [2]. Over time, many other hypertonic infusions such as bicarbonate 8.4%, sodium lactate, mannitol, and hypertonic saline have been used.

For decades, mannitol has been considered the gold standard even without consistent evidence of benefit [3]. However, more recently, there has been a controversy (the so-called sugar or salt debate) regarding the potential superiority of hypertonic saline over mannitol in several clinical settings. Still, further research is warranted to find out the optimal agent, their best means of administration (boluses vs. continuous infusion), and their precise mechanism of action [4].

In Fig. 1, we illustrate the primary mechanism of action proposed for the hyperosmolar solutions.

Mannitol

Mannitol ($C_6H_{14}O_6$) is an isomer of sorbitol found in many fruits and vegetables and has been industrially manufactured from the hydrogenation of fructose and glucose [4].

Due to its small molecular weight (182 Daltons), it is readily filtered by the glomerulus. It doesn't undergo biotransformation and is almost entirely excreted in the urine after 24 h, with only 7% being reabsorbed [4, 5].

In animal models, it inhibits the renin-angiotensin system and acts as a free radical scavenger, reducing ischemia-reperfusion lesions [5]. Therefore, it is used in distinct clinical settings, such as cardiopulmonary bypass, aortic cross-clamping, renal transplantation, rhabdomyolysis, and obstructive jaundice [5]. Whereas low mannitol doses have a renal vasodilator effect, improving glomerular filtration rate, higher doses can cause the opposite effect [6].

Mannitol 20% (means that it provides 200 g/L) has approximately the same osmolarity as hypertonic saline 3.2% (1098 mOsm/L). After an intravenous bolus administration, it is distributed primarily in the extracellular compartments. It has an onset of action after 15 min, reaching its maximal effect in 45 min and lasting up to 6 h, with a half-life of 70–100 min [5].

Mechanisms of Action

Three mechanisms have been suggested to explain how mannitol can decrease ICP [5].

First, it transiently increases cerebral blood volume and improves cerebral perfusion pressure. Due to its rheological properties, increasing red blood cell deformability, and decreasing blood viscosity, it enhances oxygen delivery and microvascular flow to the cerebral tissues [7].

Second, reflex vasoconstriction of cerebral arterioles occurs in response to this increment in the microvascular oxygen delivery. Attention should be caught since it may not happen when the blood-brain barrier is not intact, or the cerebral autoregulation is not preserved [8].

Third, a decrease in cerebral blood volume and osmotic dehydration of the brain takes place, alleviating cerebral edema and ameliorating intracranial compliance [5].

In addition to that, Orešković et al. studied the cerebral spinal fluid (CSF) pressures in animal models and proposed a new mechanism for mannitol action based on CSF pressure variation. They suggested that an osmotic retrieval of water from the CSF into the blood circulation occurs predominantly in the spinal part of the system and increases the CSF circulation, leading to a drop in CSF pressure that begins very fast and lasts up to 40 min [9].

Mannitol and the Cardiovascular System

The hemodynamic response to an intravenous bolus of mannitol is typically triphasic [5].

Firstly, after 15 min, due to a sharp elevation in serum osmolarity, there is a rapid increase in intravascular volume. Consequently, there is a significant increment in cardiac output and pulmonary capillary wedge pressure [5].

Secondly, after 45 min approximately, there is a drop in the intravascular volume below the baseline values. It occurs due to vasodilation that takes place primarily in skeletal muscles and can cause severe hypotension with increased lactate levels. Osmotic diuresis can worsen this phenomenon due to depletion of blood volume and should be carefully monitored. It is crucial to avoid arterial hypotension since it can decrease cerebral perfusion pressure [4].

Thirdly, these hemodynamic variables return to the baseline levels [5].

Mannitol and the Kidneys

As mannitol passes into the nephron, an impairment in water reabsorption occurs in both the proximal convolute tubule and the descending limb of the loop of Henle due to its increased osmotic pressure. Next, there is a progressive reduction in sodium reabsorption in the ascending limb of the loop of Henle and the collecting tube. Hence, there is a dilution of tubular sodium concentration, preventing water from being reabsorbed back into the circulation and resulting in increased diluted urine output [4, 5].

Mannitol also activates the endogenous natriuretic peptide and suppresses the antidiuretic hormone release. Augmenting medullary blood flow dissipates medullary hypertonicity, inhibits tubular reabsorption of salt and water, and results in osmotic diuresis [5].

Around 6–12% of the patients can develop acute renal injury [10, 11]. It usually occurs in patients receiving daily or cumulative doses of mannitol higher than 200 g and 1100 g, respectively, and after 12 h and 7 days (typically within the first 48 h) when serum osmolarity exceeds 320 mOsm/L. Therefore, a high serum concentration of mannitol may be related to it [5].

Since mannitol dosage is not readily available, the osmolal gap can be used instead [12]. This surrogate measure is especially needed for elderly patients with poor neurologic status, with diabetes, in use of diuretics, and with arterial hypotension or sepsis, which are independent predisposing factors for mannitol nephrotoxicity [5]. In case of reaching an osmolal gap higher than 55 mOsm/kg, which corresponds to a mannitol concentration higher than 1000 g/dL, it is advisable to discontinue its infusion and perform hemodialysis, if necessary [5].

The mechanisms of renal injury are not entirely understood. One hypothesis is that excessive doses of mannitol lead to pronounced hypotension and peripheral vasodilation, which in turn causes renal vasoconstriction and osmotic nephrosis in patients with predisposing factors [5]. Renal vasoconstriction is particularly harmful in diabetic patients since their renal blood flow is unevenly distributed, increasing medullary susceptibility to ischemic injuries. The concomitant use of loop diuretics inhibits the compensatory mechanism of increasing sodium reabsorption in response to intravascular volume depletion, leading to a strong diuretic effect. Patients with preexisting renal disease can have a

prolonged mannitol half-like (from 70 to 100 min to more than 36 h). Therefore, it is advisable to closely monitor the intravascular volume and arterial pressure of these patients [5].

Osmotic nephrosis refers to an intracellular vacuolization caused by mannitol pinocytosis in the tubular cells of the kidney. These vacuoles eventually fuse with lysosomes and reduce the proximal tubule's lumen diameter, leading to unpredictable sequelae [5].

Hydroelectrolyte and Acid-Base Changes

Mannitol infusion typically induces a hypokalemic and hypochloremic alkalosis with volume contraction caused by excessive diuresis [13], but dilutional metabolic acidosis can also occur due to a solvent drag mechanism [5].

It is expected that for each increase in 100 g/dL in the mannitol serum concentration, the plasmatic sodium falls between 1.6 and 2.6 mEq/L and that for each increase of 182 mg/L in mannitol serum concentration, serum osmolarity increases by 10 mOsm/L. Thus, its repeated administration can cause hypertonic hyponatremia. Hence, it is not recommended to replace sodium to correct this hyponatremia because it would further increase the serum osmolarity. Hyponatremia usually is self-corrected within 3 h after an infusion of up to 1.4 g/kg of mannitol in a patient with normal renal function due to diuresis. If it doesn't occur and osmolarity reaches 310 mOsm/L or more, it is advisable to immediately stop mannitol infusion and proceed to hemodialysis if necessary [5].

Mannitol facilitates renal excretion of magnesium, potassium, phosphate, and bicarbonate ions. Whereas moderate doses (1 g/kg) of mannitol infusion usually result in mild hypokalemia, higher doses (2 g/kg) can cause hyperkalemia, especially when administrated concomitantly with blood [5]. It can occur due to hemolysis, dilutional acidosis, and a shift of potassium ions from the intracellular into the extracellular space [5].

Diabetic patients or those receiving glucocorticoids may develop a hyperglycemic hyperosmolar state related to mannitol infusion. It can manifest as an unexplained seizure, a new neurological deficit, or confusion [14].

Rebound Phenomenon and Other Concerns

For decades there has been controversy regarding the possibility that a rebound increase in ICP could occur in patients who received mannitol. The rationality for it is that mannitol can cross the blood-brain barrier and accumulate in the brain since its reflection coefficient (that describes the relative impermeability to an intact blood-brain barrier) for mannitol is 0.9. Therefore, it may accumulate in injured brain regions after prolonged infusions, leading to a reverse osmotic shift and rebound ICP elevation [4]. However, this phenomenon has only been demonstrated in rats, and its relevance in humans is still unknown [15].

In addition to that, patients receiving prolonged hyperosmolar infusions can produce and accumulate cerebral idiogenic osmoles that also simulate a rebound phenomenon. The astrocytes provide them in an attempt to equilibrate the osmotic gradient generated. It can possibly explain the need for higher dosages of hyperosmotic infusions to reach the same effect when the treatment lasts several days. Therefore, it is also a concern in patients receiving hypertonic saline solutions [5, 16].

Mannitol use should be carefully monitored or even contraindicated when there is a possibility that the blood-brain barrier is disrupted, such as in patients with severe traumatic brain injuries, intracerebral hemorrhage, or vasogenic edema [5]. When cerebral autoregulation is not preserved, the transient increase in cerebral blood flow that occurs right after mannitol infusion may not be followed by cerebral vasoconstriction, leading to undesirable cerebral hyperemia [5].

Finally, there is also a concern that, since the therapeutic reduction in water content occurs predominantly in undamaged regions of the brain, hyperosmolar treatment could potentially exacerbate pressure gradients within the skull and lead to herniations. Accordingly, modern image techniques can detect slight displacements in brain structures, but they seem to have little clinical relevance [14].

Mannitol Dosages

Oddo M et al. acknowledged in their meta-analysis that mannitol bolus was associated with a reduction in the ICP of approximately 10.9 mmHg (95%CI = 8.2–13.5 mmHg, $p < 0.001$). Heterogeneity was high, but sensitivity analysis using a high correlation between before and after measurements corroborated this finding. By meta-regression, the extent of ICP reduction had no correlation to mannitol dosage. However, after adjusting for initial ICP, they found that for every 100 mg/kg of mannitol administration, there was a decrease of 0.78 mmHg in ICP ($p < 0.003$) [17].

A reasonable dosage of mannitol would be from 0.25 to 1 g/kg [18]. Other authors claim that it is safe to administer mannitol boluses from 0.15–0.2 g/kg up to 2 g/kg over 30–60 min [5]. However, it is crucial to avoid its prolonged administration, as mentioned before in this chapter, due to the formation of cerebral idiogenic osmoles and potential nephrotoxicity. As serum mannitol dosage is not readily available, when reaching an osmolar gap higher than 55 mOsm/kg or a serum osmolarity higher than 320 mOsm/L, mannitol infusion should be immediately discontinued. It is also recommended to avoid the administration of more than 200 g of mannitol per day or cumulative doses higher than 1100 g [5].

Hypertonic Saline

Even though mannitol has been considered the gold standard hyperosmolar agent for decades, hypertonic saline has recently gained popularity. One of its main advantages is not crossing the blood-brain barrier (its reflection coefficient is 1), which means that it doesn't accumulate in the brain tissue [18]. It seems to be as much or even more advantageous than mannitol in several clinical settings. Apart from it, patients who do not respond to mannitol may benefit from repeated boluses of hypertonic saline [19].

Hypertonic saline is the hyperosmolar solution of normal saline. It is usually available at 3 (or 3.2)%, 5%, 7.5%, and 23% concentrations. As a hypertonic solution, it can ameliorate cerebral perfusion and diminish cerebral edema, decreasing ICP. Different from mannitol, it doesn't cause a strong diuretic response. Thus, it generates a prolonged expansion of the intravascular volume, which may be highly desirable in hypovolemic patients. However, it may be hazardous for cardiac heart failure patients since it can precipitate acute pulmonary edema [4].

It doesn't cross the blood-brain barrier; therefore, it doesn't penetrate the brain tissue, remaining in the intravascular compartment [4, 5]. When used in concentrations higher than 3% through a peripheral cannula, it can lead to extravasation injuries, such as thrombophlebitis and subcutaneous infiltration [4].

Mechanisms of Action

As a hyperosmolar agent, its classical mechanism of action has been attributed to reducing brain water content due to its osmotic properties. Thus, it shares the favorable rheologic and osmolar gradient effects involved in ICP reduction with mannitol [20]. However, a sustained decrease in ICP appears to occur even after serum sodium values return to levels that its osmotic effect is no longer expected to be active. Thus, other mechanisms seem to be involved [21].

Several theories have been proposed. Hypertonic saline seems to restore Na/glutamate release, which has an undesirable toxic excitatory effect in the injured brain [22]. It also appears to normalize cellular resting membrane potential and cell volume [16, 23], stimulate arterial natriuretic peptide [24], inhibit neuroinflammation [25], and reduce CSF production [21].

Another postulated mechanism of its action for ameliorating cerebral edema is the down-regulation of aquaporin-4 expression in the astrocytes [26].

HTS and Cardiovascular System

Aiming to observe the cardiovascular effects of HTS, healthy volunteers with average vascular permeability had their cardiovascular parameters studied. After an infusion of 4 ml/kg of hypertonic saline 7.5% as a single dose over 30 min, an increase of plasma volume was noticeable, equiv-

alent to almost twice the infused volume. There was also an increase in the cardiac index, mean arterial pressure, and heart rate. However, stroke volume didn't seem to change significantly. A significant increase in the extracellular and intravascular volumes from the baseline was reported and suggested to be partially achieved due to the shift of water from the intracellular into the extracellular compartment. The researchers also acknowledged that interstitial water initially decreased during the infusion of HTS and then began to increase, reaching higher levels than the baseline at the end of the procedure [22].

Hypertonic saline infusion rapidly increases intravascular volume. Thus, it should be used cautiously in patients with cardiac heart failure or any other condition that a volume overload is potentially harmful. Concomitant use of furosemide can mitigate this risk [14].

HTS and the Kidneys

Acute kidney injury has been reported in up to 16% of patients who received NaCl 3% continuous infusion in neurocritical care settings. It is associated with prolonged ICU stay and higher inhospital mortality [27]. Even though bolus administration seems to be less harmful, there is not enough evidence to support one dosing strategy over the other [28].

Whereas mannitol may cause renal injury mainly because of hypovolemia due to excessive diuresis, hypertonic saline appears to be nephrotoxic through a different mechanism, mediated by hypernatremia and hyperchloremia. Raised sodium and chloride concentrations can cause renal vasoconstriction and, thereby, impair renal perfusion [29].

Hydroelectrolyte and Acid-Base Changes

The impact of HTS on acid-base balance is not entirely understood. It can cause mild acidosis, which may stimulate respiratory drive. It can also be associated with hyperchloremia and other hydroelectrolyte disturbances [4, 14].

Therefore, it is highly recommended to monitor renal function and electrolytes in patients receiving hypertonic saline infusions [30]. Hyperchloremia (Cl > 110 mEq/L), hyperosmolarity, and severe hypernatremia (Na > 155 mEq/L) are apparently related to acute renal injury [28].

Hypernatremia is a critical concern since it poses a theoretical risk of osmotic demyelination (formerly called central pontine myelinolysis) when serum sodium levels rise very quickly, especially in hyponatremic patients [31]. It is noticeable that elevated ICP conditions are commonly associated with SIAD (syndrome of inappropriate antidiuretic hormone secretion) and cerebral waste syndrome. Hence, close monitoring of serum sodium levels, sometimes every 4 or 2 h, is advisable [31].

HTS Dosages

In their meta-analysis, Oddo et al. reported that hypertonic saline infusion was associated with an average ICP reduction of 8.8 mmHg (95%CI = 6.5–11.1 mmHg, $p < 0.001$). The dose was not a predictor of ICP reduction. However, the inclusion of the initial ICP together with the dose in a multivariate meta-regression approach generated statistically significant slopes [17].

There is not enough evidence in the literature regarding the benefit of targeting a specific serum sodium concentration when administering hypertonic saline. Instead, it is advisable to constantly monitor neurological symptoms, ICP (when possible), and sodium changes to adjust the treatment accordingly [28].

Half-Molar Sodium Lactate (SL-Totilac™ Innogene Kalbiotech, Singapore, Malaysia) or Hypertonic Lactate (HL)

An alternative to hypertonic saline or mannitol to treat elevated ICP, hypertonic lactate, also called half-molar sodium lactate (SL-Totilac™ Innogene Kalbiotech, Singapore, Malaysia), has been recently studied. Apart from being a hyperosmolar solution, its effects cannot be only attributed to the classical osmotic mechanism of action since lactate also seems to be involved [32].

Lactate is one major oxidative substrate produced by injured brain cells. It has a unique role in

Table 1 Hypertonic solutions

	Mannitol 20%	Hypertonic saline
Cardiovascular system	Phase 1 (after 15 min): rapid increase in intravascular volume Phase 2 (after 45 min): drop in intravascular volume below the baseline values due to vasodilation and osmotic diuresis	Prolonged and rapid expansion of the intravascular volume—caution should be taken in patients with cardiac heart failure or conditions in which a volume overload could be deleterious
Acute kidney injury	6–12%; associated with high serum concentration of mannitol (surrogate measure: osmolal gap higher than 55 mOsm/kg	Up to 16%; mechanism mediated by hypernatremia and hyperchloremia
Hydroelectrolyte and acid-base changes	Hypokalemic and hypochloremic alkalosis with volume contraction Hypertonic hyponatremia (usually self-corrected) Risk of hyperglycemic hyperosmolar state	Hypernatremia (risk of osmotic demyelination) Hyperchloremia, mild acidosis
Concerns	It shouldn't be used in patients with any suspicious of rupture of the blood-brain barrier and loss of cerebral autoregulation	Pediatrics patients- sustained (>72 h) serum sodium greater than 160 mEq/L may be associated with thrombocytopenia, anemia, and deep vein thrombosis
	Rebound phenomenon Accumulation of cerebral idiogenic osmoles in prolonged infusions	It doesn't seem to cross the blood-brain barrier but also can induce cerebral idiogenic osmole formation in prolonged infusions

inducing cerebral vasodilation when oxygen delivery is diminished. The brain can use lactate as an alternative energy source when there is insufficient glucose availability [33]. Furthermore, it also appears to play a role in the metabolic interaction between astrocytes and neurons [34].

Many studies have already shown the efficacy of HL in treating elevated ICP [35, 36]. One of them is a randomized controlled trial with 60 patients with severe traumatic brain injury, in which it was found that those who received 0.5 ml/kg/h of SL within the first 12 h post-trauma had fewer episodes of increased ICP compared to a control group that received normal saline [36]. The authors speculate that sodium accumulates in the extracellular space since lactate is rapidly metabolized in the brain cells. It generates an electric gradient that promotes chloride efflux from the cells. Then, there is an efflux of water from the cells to maintain the osmotic equilibrium, ameliorating the brain cellular edema [35]. Other proposed mechanisms of action for HL are improvement of cerebral hemodynamics [17, 37] and attenuation of energetic metabolic crisis [38, 39].

Despite all these evidences, ESICM (European Society of Intensive Care Medicine) consensus in 2018 didn't provide any recommendation regarding the use of HL as a first-line osmotic solution [17].

In Table 1, we summarize the main differences between mannitol and hypertonic saline.

Clinical Settings

Neuroanesthesia

Considering that a bulging of the brain can significantly lead to difficult surgical access, brain relaxation maneuvers can facilitate surgery since less retraction pressure may be required to expose and manipulate brain structures. Therefore, one of the main goals of neuroanesthesia is to provide adequate brain relaxation [18]. This refers to the content-space relationship of the intracranial cavity after opening the dura. Intracranial hypertension results in an increased volume of the brain that surpasses the capacity of the intracranial space, clearly evident

after the dura opening. Thus, a subjective evaluation by the neurosurgeons of the brain firmness after opening the dura is commonly used to assess brain relaxation status [40].

One of the standard brain relaxation maneuvers is the infusion of hyperosmolar solutions. Within minutes, there is a drop in ICP and a visible reduction of the brain volume during craniotomy. Hyperosmolar therapy effects are comparable to acute forced ventilation, with the advantage of being more consistent and longer-lasting [14].

A systematic review found an improvement in cardiac performance with both hyperosmolar agents. However, this improvement was more evident after the HTS infusion. Mannitol had a more prominent diuretic effect and induced transient hyponatremia [41].

A recent trial compared equimolar 5 ml/kg infusions of 3% HTS and 20% mannitol regarding their effects on blood coagulation. No differences were found between the two groups, as evidenced by ROTEM and standard coagulation tests. It was acknowledged an increase of CFT EXTEM, hematocrit, platelet count, and fibrinogen and a decrease of CT INTEM compared to baseline levels with both agents, but still within the normal range [42].

Intracranial Tumors

Some brain tumors cause a significant brain swelling that may occur pre-, intra-, or postoperatively. Hyperosmolar agents can improve brain elastance pre- or intraoperatively and can also be used to control ICP and cerebral edema after surgery [18].

A systematic review in 2014 suggested that HTS significantly reduces the risk of tense/swollen brain compared to mannitol during elective craniotomies, mainly for tumor resections. However, this data was derived from a limited number of studies. They pointed out the need for high-quality data concerning long-term mortality and outcomes, adverse events monitoring, and quality of life evaluation after both treatments [18].

A more recent meta-analysis also found HTS to provide a higher rate of adequate brain relaxation during craniotomies in comparison to mannitol [43].

Hyperosmotic solutions also can be used for a new approach to the treatment of brain tumors. This strategy is called blood-brain barrier disruption, and it seems to increase the delivery of antineoplastic agents to the central nervous system [44].

Neurointensive Care

Hyperosmolar agents are used to treat cerebral edema in a variety of clinical settings in neurocritical patients [12].

According to the ESICM (European Society of Intense Care Medicine) consensus, osmotherapeutic agents can be used to reduce increased ICP in neurocritical care patients. They recommend a predefined trigger based on clinical and neuromonitoring variables.

They suggest the combination of neurological worsening (defined as a decrease of two points of the GSC motor score, or loss of pupillary reactivity or asymmetry, or deterioration of head CT findings) and ICP >25. They also accept ICP > 25 without other variables but strongly recommend against the use of ICP > 15 independently of other variables as a trigger.

It is advisable to monitor ICP response and measure serum osmolarity and electrolytes, as well as fluid balance and arterial blood pressure to limit side effects of the hyperosmolar therapy. They don't recommend using HTS as a resuscitation fluid in patients with low blood pressure and report insufficient evidence to support hypertonic lactate [17].

Another guideline recently published recommended the use of hyperosmolar therapy to treat ICP elevations or cerebral edema. However, they acknowledged no compelling evidence of an improvement in neurological outcomes [12].

It is proved that the control of elevated ICP has a beneficial effect on survival. Hyperosmolar agents can be used to control intracranial hyper-

tension. However, their beneficial role on survival can only be assumed since there are no trials omitting hyperosmolar therapy from the standard treatment [14]. Outcomes may be affected by unknown or uncontrolled variables, such as comorbidities, associated injuries or complications, and rehabilitation availability [30].

Traumatic Brain Injury (TBI)

The Committee of the Brain Trauma Foundation in 2016 endorsed the use of hyperosmolar agents in the care of patients with severe TBI. Due to limited data, they didn't formally recommend one specific agent over the other. They also removed the recommendation of mannitol use for patients with signs of transtentorial herniation or progressive neurological deterioration [4].

In the setting of TBI, hypertonic saline use has more advantages than mannitol. It provides plasma volume expansion, brain cell immune modulation, and extracellular glutamate reduction and improves cerebral blood flow [5].

A recent Cochrane review compared the effect of hypertonic saline and mannitol in patients with TBI. Even though both treatments proved to be effective, there was a trend favoring HTS because it seemed to have more benefits. There was insufficient data to evaluate long-term outcomes and adverse events, such as rebound phenomenon, pulmonary edema, and acute renal failure [32].

An ongoing multicenter randomized trial (COBI—Continuous Hyperosmolar Therapy in Traumatic Brain-Injured Patients) compares the functional outcome after 6 months of patients receiving hypertonic saline 20% as an add-on to standard care versus a control group receiving only standard care. Hopefully, it will provide some new evidence regarding the long-term benefits of hypertonic saline treatment in patients with TBI [37].

Intracranial Hemorrhage

The impact of ICP lowering on neurological outcomes of patients with intracranial hemorrhages is still unknown. The main challenge is avoiding perihematomal edema expansion since it is correlated with worse neurological outcomes [12, 45, 46]. Some studies have shown a potential risk of hematoma expansion with mannitol use [12, 45, 46], but Misra and colleagues reported no significant change in horizontal or vertical shift documented by magnetic resonance imaging after mannitol administration in these patients [3, 47].

Mannitol shouldn't be used when there is a disruption of the blood-brain barrier since it can penetrate and accumulate in the brain, blunting the osmotic effects and sometimes even aggravating the cerebral edema [5].

Fortunately, some studies have shown a potential benefit of hypertonic saline in this clinical setting [12].

Acute Ischemic Stroke

The current guideline of the American Stroke Association concluded that there is not enough data to support the prophylactic use of hyperosmolar agents based only on early CT swelling without clinical evidence of elevated ICP. Indeed, the preemptive use of mannitol in this situation may even be harmful [12].

For patients with cerebral edema and clinical deterioration, osmotic therapy is reasonable. However, more data is needed to evaluate the effect of each agent depending on the clinical situation [12, 48].

In a small trial, patients with a large hemispheric infarction and a midline shift of >10 mm who received 1.5 g/kg of mannitol were evaluated. It was noticed a slight decrease in the cerebral blood flow restricted to the non-infarcted hemisphere. Thus, the midline shift tended to worsen since the shrinkage occurred mainly in the non-infarcted hemisphere [49].

Hypertonic saline appears to have a more robust and long-lasting effect than mannitol in acute ischemic stroke patients. It also seems to have a faster onset of action. Moreover, patients who didn't respond to mannitol still can have an adequate response to hypertonic saline [48].

Subarachnoid Hemorrhage

Cook and colleagues recommended using hypertonic saline in patients with subarachnoid hemorrhage due to its ability to improve brain tissue oxygenation. They suggested a symptom-based dosage and didn't identify any compelling evi-

dence to support targeting a specific serum sodium concentration while treating these patients. However, they pointed out that the overall quality of the data was low and insufficient to assess the clinical outcomes related to this treatment [12]. There is also a concern related to acute kidney injury in these patients [50].

Even though mannitol at doses varying from 0.25 to 1 g/kg can provide brain relaxation in patients undergoing craniotomies for aneurysm clipping, its effects in this setting are still controversial and need further investigation [5].

Hepatic Encephalopathy

Hyperosmolar therapy can be used as an add-on treatment for patients with fulminant liver failure and encephalopathy. Further research is warranted to investigate the influence of ammonia lowering therapy and define the optimal strategies for treating intracranial hypertension and cerebral edema in these patients [12, 51].

Neuropediatrics

There is a lack of high-quality research explicitly addressed to this population. Therefore, most practical guidelines are based on mixed disease population studies, with both children and adults.

A consortium of pediatric societies developed a comprehensive guideline for TBI pediatric patients based on the recommendations of the Brain Trauma Foundation [52]. They considered as level II recommendation (based on a moderate-quality body of evidence) the administration of boluses of hypertonic saline 3% of 2–5 ml/kg over 10–20 min for the ICP control of these patients. Continuous infusions on a sliding scale or boluses of 23.4% HTS for refractory intracranial hypertension were considered level III evidence (based on a low-quality body of evidence). Regarding safety issues, they recommended avoiding sustained (>72 h) serum sodium concentrations greater than 160 mEq/L since it was associated with complications such as thrombocytopenia, anemia, and deep vein thrombosis. They pointed out that even though mannitol is commonly used to control elevated ICP in neuropediatric patients, there is insufficient evidence to endorse it. They also reported there was not enough data to evaluate the potential beneficial effect of hyperosmotic therapy on the neurological outcomes of this population [52].

In Table 2, we summarize the main findings in the literature concerning the use of mannitol in comparison to hypertonic saline in different clinical settings.

Clinical Case

A 12-year-old female suffered a severe TBI after a car accident. When the rescue team arrived, she was awake, with normal breathing, Glasgow Coma Scale of 8, isodiametric pupils, blood pressure 160 × 80, and HR 120 bpm.

She had no comorbidities besides being overweight (55 kg). She was transferred to the hospital with spinal immobilization, and further investigation showed no medullary injuries. After 2 h of the accident, she developed a conscience level impairment, with a Glasgow Coma Scale of 5. Thus, she was sedated, intubated, and mechanically ventilated. CT scan showed large regions of frontal brain contusion with surrounding edema and no hematomas. An external ventricular drain and ICP monitoring device were placed. The initial ICP was 30 mmHg but dropped to 26 mmHg after CSF drainage. Serum sodium was 139 mmol/L, creatinine was 0.9 mg/dL, and hematocrit was 31% after initial volume stabilization.

Questions

1. Would you recommend a hyperosmolar treatment for this patient? If so, which agent would you prefer?
2. How would you prescribe it?

Discussion—based on [3, 14, 31, 52, 53]

The deteriorating neurological clinical state of this patient points out the risk of further and fatal elevations of intracranial pressure. Since there is no formal indication for neurosurgical treatment, hyperosmolar therapy is an appropriate clinical approach.

As we discussed before in this chapter, there is not enough evidence to support the use of man-

Table 2 Clinical settings: sugar or salt?

	Evidence for ICP lowering benefit	Sugar or salt	Precautions	Long-term outcome benefit	References
Neuroanesthesia	For brain relaxation	Trend toward HTS	Dehydration and HE disturbances with mannitol use	No evidence	[18, 40, 42, 43]
Intracranial tumors	Some kinds of tumors	Trend toward HTS	Rebound phenomenon with mannitol	No evidence	[18, 43, 44]
TBI	Yes, and a potential benefit of HL	Trend toward HTS	AKI and HE disturbances	No evidence yet (COBI)	[4, 5, 12, 32, 37]
Intracranial hemorrhage	Little evidence	HTS	Hematoma expansion and rebound (mannitol) AKI and HE disturbances (HTS)	No evidence	[12, 45, 46]
Acute ischemic stroke	Yes, but preemptive use is not recommended	Trend toward HTS	Decrease in CBF in the non-infarcted hemisphere	No evidence	[12, 48, 49]
Subarachnoid hemorrhage	Low evidence	HTS	AKI and HE disturbances	No evidence	[5, 12, 50]
Hepatic encephalopathy	As an add-on treatment	Both	AKI, HE disturbances (HTS), rebound (mannitol)	No evidence	[12, 51]
Neuropediatrics	Moderate evidence, mainly in TBI	HTS	Anemia, thrombocytopenia, DVT and AKI (HTS)	No evidence	[52]

HTS: hypertonic saline, TBI: traumatic Brain Injury, HL: hypertonic lactate (half-molar sodium lactate), AKI: acute kidney injury, HE: hydroelectrolyte, DVT: deep vein thrombosis, COBI: Continuous Hyperosmolar Therapy in Traumatic Brain-Injured Patients (trial)

nitol in pediatric neurocritical patients. Therefore, hypertonic saline should be more appropriate.

Hypertonic saline is usually administrated in boluses of 150 ml of the 3% solution (513 mmol/L), 75 ml of a 7.5% solution (1283 mmol/L), or 30 ml of 23.4% solution (4008 mmol/L). In pediatric patients, caution should be taken to avoid serum sodium concentrations higher than 160 mEq/L. It may be associated with deep vein thrombosis, anemia, and thrombocytopenia in concentrations higher than 170 mEq/L [52].

Calculating the amount of HTS to reach an initial target sodium concentration of approximately 150 mmol/L, the sodium requirement would be:

Na requirement = (lean body weight, in kg) × (% of the water in the bodyweight) × (desired sodium – current sodium).

Note: the percentage of water in the bodyweight is approximately 0.5 for females and 0.6 for males; since the patient was 12 years old and weighed 55 kg, we considered the value of 0.5:

Na requirement = 55 × 0.5 × (150 – 139).

Na requirement = 302 mmol.

It corresponds to 589 ml of 3% saline or 75 ml of 23% saline.

Therefore, the initial prescription could be 5 ml/kg (275 ml) of hypertonic saline 3% in 10 min, which could be repeated twice to reach an ICP of 20 mmHg. It is highly recommended to monitor serum sodium levels carefully to avoid rapid changes. Renal function, electrolytes, and gasometry should be measured at regular intervals. Moreover, subsequent boluses or continuous infusions could be administered, aiming to improve her neurological status. Extreme hyperosmolarity, as reflected by serum sodium levels higher than 160 mmol/L, is unlikely to have further beneficial effects and may even generate undesirable effects.

Take-Home Messages

- Hyperosmolar solutions can be used to treat cerebral edema in various clinical settings in neurocritical care and neuroanesthesia.
- Caution should be taken in patients with loss of cerebral autoregulation or disruption of the brain-blood barrier.
- Prolonged infusions of both hypertonic solutions can lead to the accumulation of cerebral idiogenic osmoles that can simulate a rebound phenomenon.
- The main concerns associated with mannitol use are dehydration due to osmotic diuresis, acute kidney injury due to high serum concentration of mannitol, and rebound phenomenon.
- The main concerns associated with the use of hypertonic saline are volume overload, acute kidney injury associated with hyperchloremia, and hypernatremia. Extravasation injuries can occur when administered in peripheral cannulas.

References

1. Weed L. Experimental alteration of brain bulk. In: McKibben P, editor. Am J Phys.1919. p. 531–558.
2. JAVID M, SETTLAGE P. Effect of urea on cerebrospinal fluid pressure in human subjects; preliminary report. J Am Med Assoc. 1956;160(11):943–9.
3. Misra UK, Kalita J, Goyal G. Hyperosmolar therapy for raised intracranial pressure. N Engl J Med. 2012;367(26):2554–5. author reply 6-7
4. Freeman N, Welbourne J. Osmotherapy: science and evidence-based practice. BJA Educ. 2018;18(9):284–90.
5. Fandino W. Understanding the physiological changes induced by mannitol: from theory to the clinical practice in neuroanaesthesia. J Neuroanaesthesiol Crit Care. 2017;4:138–46.
6. Nomani AZ, Nabi Z, Rashid H, Janjua J, Nomani H, Majeed A, et al. Osmotic nephrosis with mannitol: review article. Ren Fail. 2014;36(7):1169–76.
7. Burke AM, Quest DO, Chien S, Cerri C. The effects of mannitol on blood viscosity. J Neurosurg. 1981;55(4):550–3.
8. Rosner MJ, Coley I. Cerebral perfusion pressure: a hemodynamic mechanism of mannitol and the postmannitol hemogram. Neurosurgery. 1987;21(2):147–56.
9. Orešković D, Maraković J, Varda R, Radoš M, Jurjević I, Klarica M. New insight into the mechanism of mannitol effects on cerebrospinal fluid pressure decrease and craniospinal fluid redistribution. Neuroscience. 2018;392:164–71.
10. Gondim FA, Aiyagari V, Shackleford A, Diringer MN. Osmolality not predictive of mannitol-induced acute renal insufficiency. J Neurosurg. 2005;103(3):444–7.
11. Lin SY, Tang SC, Tsai LK, Yeh SJ, Shen LJ, Wu FL, et al. Incidence and risk factors for acute kidney injury following mannitol infusion in patients with acute stroke: a retrospective cohort study. Medicine (Baltimore). 2015;94(47):e2032.
12. Cook AM, Morgan Jones G, Hawryluk GWJ, Mailloux P, McLaughlin D, Papangelou A, et al. Guidelines for the acute treatment of cerebral edema in neurocritical care patients. Neurocrit Care. 2020;32(3):647–66.
13. Better OS, Rubinstein I, Winaver JM, Knochel JP. Mannitol therapy revisited (1940–1997). Kidney Int. 1997;52(4):886–94.
14. Ropper AH. Hyperosmolar therapy for raised intracranial pressure. N Engl J Med. 2012;367(8):746–52.
15. Zeng HK, Wang QS, Deng YY, Jiang WQ, Fang M, Chen CB, et al. A comparative study on the efficacy of 10% hypertonic saline and equal volume of 20% mannitol in the treatment of experimentally induced cerebral edema in adult rats. BMC Neurosci. 2010;11:153.
16. McManus ML, Soriano SG. Rebound swelling of astroglial cells exposed to hypertonic mannitol. Anesthesiology. 1998;88(6):1586–91.
17. Oddo M, Poole D, Helbok R, Meyfroidt G, Stocchetti N, Bouzat P, et al. Fluid therapy in neurointensive care patients: ESICM consensus and clinical practice recommendations. Intensive Care Med. 2018;44(4):449–63.
18. Prabhakar H, Singh GP, Anand V, Kalaivani M. Mannitol versus hypertonic saline for brain relaxation in patients undergoing craniotomy. Cochrane Database Syst Rev. 2014;7:CD010026.
19. Horn P, Münch E, Vajkoczy P, Herrmann P, Quintel M, Schilling L, et al. Hypertonic saline solution for control of elevated intracranial pressure in patients with exhausted response to mannitol and barbiturates. Neurol Res. 1999;21(8):758–64.
20. Muizelaar JP, Wei EP, Kontos HA, Becker DP. Cerebral blood flow is regulated by changes in blood pressure and in blood viscosity alike. Stroke. 1986;17(1):44–8.
21. Mortazavi MM, Romeo AK, Deep A, Griessenauer CJ, Shoja MM, Tubbs RS, et al. Hypertonic saline for treating raised intracranial pressure: literature review with meta-analysis. J Neurosurg. 2012;116(1):210–21.
22. Järvelä K, Koskinen M, Kööbi T. Effects of hypertonic saline (7.5%) on extracellular fluid volumes in healthy volunteers. Anaesthesia. 2003;58(9):878–81.
23. Nakayama S, Kramer GC, Carlsen RC, Holcroft JW. Infusion of very hypertonic saline to bled rats:

membrane potentials and fluid shifts. J Surg Res. 1985;38(2):180–6.
24. Arjamaa O, Karlqvist K, Kanervo A, Vainionpää V, Vuolteenaho O, Leppäluoto J. Plasma ANP during hypertonic NaCl infusion in man. Acta Physiol Scand. 1992;144(2):113–9.
25. Qureshi AI, Suarez JI. Use of hypertonic saline solutions in treatment of cerebral edema and intracranial hypertension. Crit Care Med. 2000;28(9):3301–13.
26. Zeng HK, Wang QS, Deng YY, Fang M, Chen CB, Fu YH, et al. Hypertonic saline ameliorates cerebral edema through downregulation of aquaporin-4 expression in the astrocytes. Neuroscience. 2010;166(3):878–85.
27. Riha HM, Erdman MJ, Vandigo JE, Kimmons LA, Goyal N, Davidson KE, et al. Impact of moderate hyperchloremia on clinical outcomes in intracerebral hemorrhage patients treated with continuous infusion hypertonic saline: a pilot study. Crit Care Med. 2017;45(9):e947–e53.
28. Maguigan KL, Dennis BM, Hamblin SE, Guillamondegui OD. Method of hypertonic saline administration: effects on osmolality in traumatic brain injury patients. J Clin Neurosci. 2017;39:147–50.
29. Narayan SW, Castelino R, Hammond N, Patanwala AE. Effect of mannitol plus hypertonic saline combination versus hypertonic saline monotherapy on acute kidney injury after traumatic brain injury. J Crit Care. 2020;57:220–4.
30. Asehnoune K, Lasocki S, Seguin P, Geeraerts T, Perrigault PF, Dahyot-Fizelier C, et al. Association between continuous hyperosmolar therapy and survival in patients with traumatic brain injury - a multicentre prospective cohort study and systematic review. Crit Care. 2017;21(1):328.
31. Moritz ML, Ayus JC. Hyperosmolar therapy for raised intracranial pressure. N Engl J Med. 2012;367(26):2555–6. author reply 6-7
32. Chen H, Song Z, Dennis JA. Hypertonic saline versus other intracranial pressure-lowering agents for people with acute traumatic brain injury. Cochrane Database Syst Rev. 2020;1:CD010904.
33. Gordon GR, Choi HB, Rungta RL, Ellis-Davies GC, MacVicar BA. Brain metabolism dictates the polarity of astrocyte control over arterioles. Nature. 2008;456(7223):745–9.
34. Roquilly A, Mahe PJ, Latte DD, Loutrel O, Champin P, Di Falco C, et al. Continuous controlled-infusion of hypertonic saline solution in traumatic brain-injured patients: a 9-year retrospective study. Crit Care. 2011;15(5):R260.
35. Ichai C, Armando G, Orban JC, Berthier F, Rami L, Samat-Long C, et al. Sodium lactate versus mannitol in the treatment of intracranial hypertensive episodes in severe traumatic brain-injured patients. Intensive Care Med. 2009;35(3):471–9.
36. Ichai C, Payen JF, Orban JC, Quintard H, Roth H, Legrand R, et al. Half-molar sodium lactate infusion to prevent intracranial hypertensive episodes in severe traumatic brain injured patients: a randomized controlled trial. Intensive Care Med. 2013;39(8):1413–22.
37. Shackford SR, Zhuang J, Schmoker J. Intravenous fluid tonicity: effect on intracranial pressure, cerebral blood flow, and cerebral oxygen delivery in focal brain injury. J Neurosurg. 1992;76(1):91–8.
38. Vespa P, Bergsneider M, Hattori N, Wu HM, Huang SC, Martin NA, et al. Metabolic crisis without brain ischemia is common after traumatic brain injury: a combined microdialysis and positron emission tomography study. J Cereb Blood Flow Metab. 2005;25(6):763–74.
39. Oddo M, Levine JM, Frangos S, Maloney-Wilensky E, Carrera E, Daniel RT, et al. Brain lactate metabolism in humans with subarachnoid hemorrhage. Stroke. 2012;43(5):1418–21.
40. Li J, Gelb AW, Flexman AM, Ji F, Meng L. Definition, evaluation, and management of brain relaxation during craniotomy. Br J Anaesth. 2016;116(6):759–69.
41. Tsaousi G, Stazi E, Cinicola M, Bilotta F. Cardiac output changes after osmotic therapy in neurosurgical and neurocritical care patients: a systematic review of the clinical literature. Br J Clin Pharmacol. 2018;84(4):636–48.
42. Hernández-Palazón J, Fuentes-García D, Doménech-Asensi P, Piqueras-Pérez C, Falcón-Araña L, Burguillos-López S. Equiosmolar solutions of hypertonic saline and mannitol do not impair blood coagulation during elective intracranial surgery. J Neurosurg Anesthesiol. 2017;29(1):8–13.
43. Fang J, Yang Y, Wang W, Liu Y, An T, Zou M, et al. Comparison of equiosmolar hypertonic saline and mannitol for brain relaxation during craniotomies: a meta-analysis of randomized controlled trials. Neurosurg Rev. 2018;41(4):945–56.
44. Blanchette M, Fortin D. Blood-brain barrier disruption in the treatment of brain tumors. Methods Mol Biol. 2011;686:447–63.
45. Sun S, Li Y, Zhang H, Wang X, She L, Yan Z, et al. The effect of mannitol in the early stage of supratentorial hypertensive intracerebral hemorrhage: a systematic review and meta-analysis. World Neurosurg. 2018;S1878–8750(18):32818–3.
46. Aminmansour B, Tabesh H, Rezvani M, Poorjafari H. Effects of mannitol 20% on outcomes in nontraumatic intracerebral hemorrhage. Adv Biomed Res. 2017;6:75.
47. Misra UK, Kalita J, Ranjan P, Mandal SK. Mannitol in intracerebral hemorrhage: a randomized controlled study. J Neurol Sci. 2005;234(1–2):41–5.
48. Schwarz S, Georgiadis D, Aschoff A, Schwab S. Effects of hypertonic (10%) saline in patients with raised intracranial pressure after stroke. Stroke. 2002;33(1):136–40.
49. Videen TO, Zazulia AR, Manno EM, Derdeyn CP, Adams RE, Diringer MN, et al. mannitol bolus preferentially shrinks non-infarcted brain in patients with ischemic stroke. Neurology. 2001;57(11):2120–2.
50. Sadan O, Singbartl K, Kandiah PA, Martin KS, Samuels OB. Hyperchloremia is associated with acute

kidney injury in patients with subarachnoid hemorrhage. Crit Care Med. 2017;45(8):1382–8.
51. Farrokh S, Cho SM, Suarez JI. Fluids and hyperosmolar agents in neurocritical care: an update. Curr Opin Crit Care. 2019;25(2):105–9.
52. Kochanek PM, Tasker RC, Carney N, Totten AM, Adelson PD, Selden NR, et al. Guidelines for the management of pediatric severe traumatic brain injury, third edition: update of the Brain Trauma Foundation guidelines. Pediatr Crit Care Med. 2019;20(3S Suppl 1):S1–S82.
53. Huh JW, Priestley MA, Dominguez TE. Hyperosmolar therapy for raised intracranial pressure. N Engl J Med. 2012;367(26):2555. author reply 6-7