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# Osmotherapy in patients with severe brain trauma: which agents should we take into account?

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## ABSTRACT

Traumatic brain injury is still a major cause of mortality and morbidity in the world and is considered a public health problem that needs to be well attended to. Cerebral oedema due to brain injury compromises the delivery of essential nutrients and alters normal intracranial pressure, whose increase has been shown to be strongly associated with poor neurological outcomes and mortality for patients with head trauma. Intravenous fluids are a fundamental component of trauma care and fluid management influences patient outcomes. Thanks to advances in the research of osmotic agents, mortality has been reduced and there has been greater control in intracranial pressure. The osmotic agents most used for the control of intracranial pressure in patients who have suffered severe brain trauma are mannitol and hypertonic saline. However, in recent years have been studying the benefits that sodium lactate can generate in these cases. It has been found that sodium lactate has generated a greater decrease in intracranial pressure values and lower mortality rates with respect to mannitol and hypertonic saline. This still has been disputed as an application of mannitol, hypertonic saline or sodium lactate for treating patients who have suffered some head trauma. This review aims to show the advantages, disadvantages and recommendations of the different hyperosmolar solutions mentioned previously based on current evidence.

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**Keywords**  
osmotherapy,  
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## INTRODUCTION

Severe traumatic brain injury (TBI) initially causes an injury to the brain by an impact as force propagates towards the cranial cavity, resulting in a stretching and loosening of neural and vascular structures. These direct injuries into the brain parenchyma or blood vessel, prompt inflammation or edema which can be accompanied by bleeding; all these factors ultimately result in an increase in intracranial pressure (ICP) (1,2).

Fluid resuscitation in patients with severe head trauma is vital because of the need to avoid hypotension and secondary neurological injury (3). The increased ICP can generate several consequences. On one hand, as the ICP increases, the cerebral perfusion pressure (CPP) (initially conserved by regulatory mechanisms) when stopping the self-regulating capacity, the CPP will decrease, which implies a risk of secondary hypoxic brain injury. Moreover, the brain can herniate between intracranial compartments and can also lead to secondary brain injury compression and territorial arterial ischemia or by direct compression of the brainstem, becoming in a very mortal issue (1). The main objective of osmotherapy is to preserve or restore the physiology and minimize secondary brain damage, through conservation of CPP and decreased ICP. Moreover, the brain tissue tension of oxygen (PbtO<sub>2</sub>) has emerged adds as an additional therapeutic goal in the treatment of these patients (3-5).

Osmotherapy has limited efficacy, so prophylactic use should be avoided and must be carefully removed after the maximum period of edema (6). In addition, it is important to pay attention to signs of rebound edema (7). The major hyperosmolar solutions used in patients with traumatic brain injury include hypertonic saline, mannitol and sodium lactate (2). In view of the above, the objective of this review is to synthesize evidence on the use of osmotherapy in the management of patients with traumatic brain injury and related aspects.

## METHODS

A bibliographic search was carried out in the PubMed and Science Direct databases and in the Google Scholar search engine using the following terms: "Osmotherapy"; "Traumatic Brain Injury"; "Intracranial Pressure"; "Mannitol"; "Sodium Lactate";

"Hypertonic Saline Solution". Articles in Spanish and English were included, emphasizing in the benefits of different osmotic agents in the treatment of severe brain trauma, regardless of the publication date. A total of 325 articles were identified from original articles, topic reviews, systematic reviews, letters to the editor, case reports, and case series. 41 articles were selected (3 in Spanish and 38 in English) that were adjusted to the objective of the article.

## RESULTS

### Mannitol

Mannitol is an osmotic agent associated with the treatment of intracranial hypertension (IH), used for clinical purposes in 1962 (3). Currently it is highlighted among its indications decreasing refractory ICP, elevated ICP, oliguria and in some cases of acute renal failure. Concentrations ranging from 5% g/100 ml at 25% g/100 ml at an osmolality between 274 and 1372 mOsm/l. As for the dose, it was observed a significant reduction in ICP and more durable responses to treatment when doses are administered between 0.5 and 1.4 g/kg (8,9). The objective is to maintain osmotherapy normal volemia or mild hypervolemia, and maintain serum osmolality between 300 and 320 mOsm/l, so particular vigilance is required to treatment (3,10,11). Mannitol acts on IH after about 20 minutes to be administered and reaches its maximum effect in the brain 30 minutes after; effect duration ranging from 90 minutes to 6 hours depending on the etiology. By decreasing the blood viscosity and the hematocrit and increase the flow of oxygenated blood brain leads to vasoconstriction of cerebral arterioles, and this in turn leads to a reduction in ICP and increasing the CPP. Broadly speaking, also generates a reduction in systemic vascular resistance (and afterload) combined with a transient increased preload and a slight positive inotropic effect, therefore, it improves cardiac output and ventilation (3,12). However, osmotic diuresis with mannitol can cause intravascular dehydration and hypotension (7). In the brain, the mannitol remains in the vascular fluid compartment (13); after prolonged use, it may cross the blood brain barrier and accumulate in the brain tissue, causing an inverse osmotic change, which increases ICP (rebound phenomenon) (7).

Mannitol is filtered at the glomerulus and reabsorbed in the nephron as an osmotic diuretic, it

is excreted unchanged (3). It can induce acute renal failure (ARF) due to renal vasoconstriction, decreased intravascular volume and hyperosmolarity (4). Usually it produces no permanent injury; then removing the drug this is reversed. Several studies report the lowest total dose of mannitol that can cause ARF is 200 g/day (3). Other side effects include electrolyte disorders (hyponatremia, hypochloremia, hyperkalemia), acidosis, heart failure and pulmonary edema (3,7). Restrict the use of mannitol in patients with signs of trans-tentorial hernia or progressive neurological deterioration causes not attributable to extracranial (14).

### **Hypertonic saline**

Hypertonic saline (HS) was used in clinical practice for the first time in 1926 by Silver, who used a 5% HS to treat Burger's disease. Currently, it is positioned as the most popular osmo-agent for hyperosmolar therapy, this due to the multiple complications associated with the use of mannitol (3,15). Continuous HS can be early to reduce brain swelling and IH (16). It is also used in cases of subarachnoid hemorrhage, stroke and liver failure. It is used as adjunctive therapy with mannitol or as an alternative treatment in those patients who failed prior therapy with mannitol (3,7,17).

It is offered in different concentrations (2%, 3%, 7.5% and 23.4%) and is recommended to administer via a central line and should be used at a concentration > 2%, avoiding the risk of thrombophlebitis and peripheral venous thrombosis (3). It is commonly administered as a bolus of 30 ml saline 23.4% (7) or in addition to continuous infusion therapy, decreasing the ICP over a period <72 hours, but this effect extended not maintained for a while (3). Similar to the action of mannitol, HS causes the liquid passage from the parenchyma into the intravascular space, reduces the rate of cerebrospinal fluid (CSF) production and having a lower diuretic effect causes expansion of the intravascular volume, increasing cerebral blood flow and reducing the ICP at the same time. also it has an anti-inflammatory effect reducing leukocyte adhesion (3,18,19). Continuous and frequent use of hypertonic saline lead to the development of hyperchloremic metabolic acidosis, which can be prevented by using hypertonic Sodium/Acetate (7,20). Other problems include ARF, arrhythmias, hemolysis and acute pulmonary edema (3).

### **Mannitol vs. hypertonic saline**

Mannitol and HS are the two most commonly used hyperosmolar solutions (7). No Class I evidence showing the superiority of one over another in the treatment of cerebral edema and intracranial hypertension of different etiologies in critically ill patients (3,21). In 2012, Mortazavi *et al.* (22) performed a meta-analysis studying the results of HS for the management and control of IH. This review included 36 articles; of these, 9 showed that HS controlled IH better, compared to mannitol. In 6 articles, a reduction in ICP values was present when HS was administered after the use of mannitol.

The potential advantages of hypertonic saline include intravascular volume expansion, to produce less osmotic diuresis, maintains a more stable patients with brain injury systemic and cerebral hemodynamics, and not only decreases the ICP and maintains the CPP, but also increases PbtO<sub>2</sub> (7,23,24). As for intracranial hemorrhage have in the acute phase there is an elevated ICP, suggesting a poor prognosis in these patients. Currently it is not known which of these two agents has better performance in this condition (3,25). There are no strong recommendations on which of the two hyperosmolar agents should be used. Mannitol is most often used as first line therapy for IH caused by cerebral trauma, as second line therapy the HS is used when no response to the first. Several authors report that both agents have a similar effect in equimolar dose, and others affirm that the HS is more efficient and safer than mannitol to decrease ICP in severe traumatic brain injury (3,26).

Although the evidence regarding these solutions and their impact on patients is low, there have been studies that have examined various aspects of these fluids with significant results. Pelletier *et al.* performed a meta-analysis which determined that when comparing the use of HS with other solutions such as mannitol, Ringer's lactate, hypertonic sodium and 0.9% saline, it was found that there is no difference in mortality and maintenance of the ICP (27).

### **Sodium lactate**

To control the elevated ICP as a result of severe brain trauma, it is necessary to use safe and effective osmotic agents. One of these has been mannitol, which has been for many years, solving lesson (27); however, there have been various adverse effects

attributable to this solution. Within these adverse effects are: hypovolemia, hypotension, renal failure, a transient effect, among others (28). Meanwhile, hypertonic saline emerged showing high efficacy in the management of patients neurocritical ill; some of the benefits that this solution is the easy monitoring of its infusion, its high potency and longer duration of effects, his great role as a stabilizer and systemic hemodynamics intracranial, among others. However, HS can cause negative effects that could limit their use; within these it has generated hypernatremia (independent marker of mortality in critically ill patients), osmotic nephropathy, phlebitis, hypokalemia, rhabdomyolysis, and many more (28,29). Therefore, in recent years it has been emerging hypertonic fluid promising for the treatment of severe IH associated with cerebral trauma, sodium lactate. To understand the mechanism of action sodium lactate, it is important to analyze the pathophysiological mechanism by which brain damage occurs in severe brain trauma. This causes trauma injuries dividing two phases: primary and secondary; said phases depend on the time elapsed since the trauma occurred (29,30). The primary stage is given the exact time when the brain injury is generated, and will be characterized by presenting vascular damage, followed by a bleeding in the brain tissue, generating a mass effect in the brain and subsequent IH. As late consequences, at this stage an imbalance of the neurotransmitter regulation, axonal damage and cell death occurs (30). In the secondary phase will be altered cerebral autoregulation mechanisms; generating power failures, which are to be supplied momentarily by increased glycolysis and oxidative phosphorylation; out of ATP stores, anaerobic metabolism begins until this process is unsatisfactory (30,31).

There is a theory that suggests that astrocytes use the process of glycolysis to lactate production; once said lactate enters neuronal cells, this is transformed into pyruvate by the action of lactate dehydrogenase, and thus involved in oxidative metabolism and energy generating (27,32). Under physiological conditions, lactate contributes 8% of the energy required by the brain; however, in cases where there is brain damage, and decreased levels of glucose, lactate can contribute over 60% (31). For this reason, sodium lactate has been a very promising method in controlling the IH in cases of severe brain trauma, requiring more research that yield firm conclusions

about the use of this solution with respect to the other, analyzing their effects beneficial and adverse effects. Sodium lactate acts primarily by decreasing the blood viscosity by increasing plasma volume, resulting in an increased blood flow and brain tissue oxygenation (31). Once increased perfusion of the brain tissue, vasoconstriction occurs reflects which contributes to decrease ICP by limiting blood supply to the brain. Due to its hypertonic properties, sodium lactate causes an increase in the osmotic pressure within the blood vessels and a great extent of osmotic gradient between the intra- and extravascular spaces. As a result, decrease the edema fluid introduced in the intravascular space, helping equally to decrease ICP (32,33).

### **Sodium lactate vs. mannitol**

In 2009, Ichai et al. (34) compared the mannitol and sodium lactate in 34 patients who had suffered traumatic brain injury and had IH; in this study it was determined that sodium lactate compared to mannitol, ICP decreased more ( $p = 0.016$ ), longer ( $p = 0.009$ ) and performed with greater success patients ( $p = 0.053$ ). In 2013, Ichai et al. (35) conducted a double-blind, randomized and controlled 60 patients who received a continuous infusion of 0.5 ml/kg/h for 48 hours sodium lactate or normal saline (control group). The results obtained showed that the sodium lactate reduced IH episodes compared to control group ( $p < 0.05$ ); this suggests that sodium lactate can be used as an alternative treatment for preventing post IH traumatic brain injury. Moreover, in patients receiving sodium lactate, better urine output and an optimal fluid balance she was found (4,31).

Within the future perspectives on osmotherapy in patients with TBI, it is necessary to mention that the use of one agent or another will vary according to the availability and level of complexity of the hospital where the patient is located (35-38). Therefore, many more studies are needed to evaluate the outcomes of the use of osmotic agents for the management of IH, according to the context of each country, team of professionals and hospital institutions (39,40). This research should be promoted more strongly in low- and middle-income countries, where there is a high incidence of neurotrauma cases, and where high-tech tools that have been shown to further improve neurosurgical outcomes of neurotrauma are not available (35,41).

## CONCLUSIONS

Traumatic brain injury is a public health problem worldwide. Management and control of intracranial hypertension back to this type of trauma has been being an aspect in which health professionals need to improve as the years pass. Osmotherapy has been a very important mechanism for achieving this objective using fluids such as mannitol and hypertonic saline, which have had great results for patients; however, there have been multiple adverse effects that affect their health. In search of better methods to treat this condition has been introduced as sodium lactate osmotherapy, which has proved very effective in counteracting the secondary damage generated by the traumatic brain injury. Similarly, it has shown better results regarding the cognitive effects after injury. However, conducting research on which these solutions are compared with respect to the benefits and disadvantages that can generate in patients is necessary.

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