Comparative efficacy analysis of mannitol and hypertonic saline in the management of traumatic brain injury: a scientific exploration of neuroprotective strategies

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Abstract

In the management of severe traumatic brain injuries (TBIs), controlling intracranial pressure (ICP) is a pivotal therapeutic goal. Historically, mannitol has been the recommended first-line osmotic agent; however, concerns surrounding its use, including hypotension, rebound ICP elevation, and renal toxicity, have prompted a quest for alternative strategies. Hypertonic saline (HS) has emerged as a promising substitute, demonstrating efficacy in reducing ICP without compromising cerebral perfusion. This comprehensive analysis explores the comparative effectiveness of Mannitol and Hypertonic Saline in the context of severe TBIs. While Mannitol has been a longstanding choice, recent attention has shifted towards HS due to its reported superiority in ICP reduction. Concerns associated with mannitol, such as hypotension and rebound ICP, are juxtaposed against the potential advantages offered by HS. The scarcity of clinical studies focusing on TBI-related outcomes, such as patient survival and long-term benefits, is highlighted, underscoring a critical gap in the current knowledge landscape. The review aims to provide a nuanced understanding of the comparative effectiveness of Mannitol and Hypertonic Saline, considering not only ICP control but also broader patient outcomes. By addressing the suitability of these agents in diverse clinical settings, this analysis seeks to guide clinicians in making informed decisions tailored to individual patient needs.

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Introduction

Traumatic Brain Injury (TBI) is on the rise as a leading cause of death and an important contributor to morbidity and mortality. As seen by declining mortality rates, medical treatment for severe TBI has advanced significantly in recent years.[1] The "silent epidemic" of increased ICP is a prevalent life-threatening illness.[2] Most neurological ailments principally traumatic brain injury can cause cerebral edema which eventually leads to the condition of Increased Intracranial Pressure (ICP). The main factor that causes death in patients with acute cerebral edema is thought to be elevated intracranial pressure also known as Intracranial Hypertension (IH).[3] Intracranial hypertension is one of the commonly seen clinical conditions in the intensive care unit which requires instant treatment. The major goal of care is to maintain normal cerebral perfusion pressure and Intracranial Pressure (ICP) to avoid secondary brain injury.[4] IH is caused by a major Central Nervous System (CNS) injury or a side effect of a concurrent systemic illness. Acute Brain Injury (ABI), which is defined as any condition affecting the central nervous system, consists of two parts: a primary brain damage that cannot be restored and a Secondary Brain Injury (SBI). Any physiological occurrence that can happen minutes, hours, or days after the initial insult and causes additional nerve damage is referred to as a SBI. Since it is primarily caused by elevated ICP, it can be identified through medical evaluation and ICP monitoring, and verified by imaging testing.[5] Several significant neurologic disorders share the pathologic state of elevated intracranial pressure, which is characterized by the addition of volume to the cranial vault.[5] The brain, cerebrospinal fluid, and blood are the three basic elements of the stiff structure known as the cranium. The pressure inside the cranial vault will rise with any increase in the volume of its contents.[6] The capacity of the human skull ranges from 1400 to 1700 mL, and it is a rather unchanging structure. According to biology, it is made up of 80% brain parenchyma, 10% cerebrospinal fluid, and 10% blood. Since the

skull is thought to be an immutable volume, any rise in the volume of its constituent parts or the inclusion of a pathologic component will lead to an increase in pressure inside the skull.[7] Increased ICP may result from cerebral edema or mass lesions in patients with Traumatic Brain Injury (TBI). Ischemia and subsequent brain damage may result from elevated ICP because it lowers Cerebral Perfusion Pressure (CPP) to the point where Cerebral Blood Flow (CBF) may deteriorate significantly.[8] TBI, stroke, intracranial hemorrhage, intracranial infection, hydrocephalus, brain tumor, as well as other neurological diseases, can all result in raised ICP as a consequence.[9] The location and degree of brain damage due to increased ICP are related to the neurological outcome, although edema or infarction of the perilesional tissue are also causally related to permanent deterioration and death.[10]

Management of the intracranial hypertension

After supportive care, which is crucial for neuroprotection, hyperosmolar treatment is the medical standard for treating ICH. Mannitol and hypertonic saline are the two osmotic agents currently used for this purpose.[11] The application of hyperosmolar solutions has been one of the main medical treatments for cerebral edema. Over the past century, there has been a significant evolution in the therapeutic targets, the medicines utilized, and how they are administered. The first to describe the ability of hyperosmolar liquids to reduce nerve tissue was Weed and McKibbens in 1919. They discovered that administering free water caused brain swelling while infusing a 30% saline solution significantly reduced brain volume.[12] Several substances, including 50% glucose, 50% sucrose, 25% sodium chloride, 25% urea, 50% magnesium sulfate, glycerol, concentrated albumin, and concentrated plasma, were examined for the purpose. The warning that "most of these dehydrating substances have only a transient effect, which may be followed by a "rebound phenomenon" during which the intracranial pressure can rise above that which existed before their administration" was included in the literature used to temper its use.[13] However, during neurosurgery or critical care unit admissions, hyperosmolar solutions are frequently used to lower ICP and brain volume.[14]

Mannitol

Brain edema can be caused by a variety of neurosurgical conditions, most notably craniocerebral trauma, which can then increase ICP. The main factor that causes mortality among individuals with acute cerebral edema is thought to be elevated pressure. Mannitol's usefulness as a regularly used medication to lower ICP has long been acknowledged.[15] 1,2,3,4,5,6-hexanehexol, often known as mannitol ($C_6H_8(OH)_6$), is a naturally occurring polyol that is largely employed for its osmotic diuretic characteristics. Mannitol decreases ICP by raising intravascular osmotic pressure, which draws extracellular fluid into the intravascular compartment since it cannot cross the endothelium membrane. By increasing plasma volume, mannitol initially reduces blood viscosity while also increasing microvascular flow and tissue oxygenation. Increased tissue perfusion causes a vasoconstriction reflex, which reduces blood flow to the brain and lowers ICP. Meanwhile, mannitol causes a rise in intravascular osmotic pressure, widening the osmotic gradient between the intravascular and extravascular compartments due to its size and difficulty in permeating through the endothelium barrier. The edematous fluid will eventually be pushed into blood vessels and significantly aid in decreasing ICP.[16] However, major adverse effects are becoming more and more evident, like rebound cerebral edema and acute renal failure. The potential negative effects of the hyperosmolar drug are to be taken into account while deciding whether to administer it. Strong diuretics like mannitol can increase the potential of injury to the kidneys in hypovolemic patients. mannitol causes osmotic diuresis, the initial quick rise in intravascular volume paradoxically has the potential to lead to acute hypervolemia and, can cause cardiac failure or pulmonary edema in vulnerable patients.[17] In the aftermath of brain damage, mannitol is frequently administered to lower elevated intracranial pressure. Initially, mannitol reduces the swelling, but there is proof that continued use over time can eventually make the pressure worse. When it comes to the pre-operative treatment of patients with acute cerebral hemorrhages, high-dose mannitol seems to be preferred to conventional-dose mannitol. The use of mannitol as a continuous infusion in patients with elevated intracranial pressure who do not have an operative cerebral hemorrhage is, however, not well supported by the available research. The ideal administration of mannitol after an acute traumatic brain injury is still a subject of much debate. Mannitol's present widespread use and the dearth of knowledge when compared with other medicines that lower intracranial pressure still require appropriate investigation.[18]

Hypertonic saline

To lower intracranial pressure after traumatic brain injury, hypertonic saline is utilized as a hyperosmolar treatment. It is still debatable whether hypertonic saline is more successful than other intracranial pressure-lowering medications in the short- and long-term therapy of acute traumatic brain injury.[19] Still, there are several potential ways for how intracranial hypertension may be treated with Hypertonic Saline (HS). By establishing a pressure gradient within the intracellular and intravascular spaces and by exhibiting some rheological effects, the HS has demonstrated a biphasic reduction in ICP. Fluid moves osmotically from the intracellular into the interstitial and intravascular area as a result of this gradient. The hypertonic saline administered must remain in the intravascular area and not penetrate the blood-brain barrier to sustain this osmotic gradient.[20] HS serves as a plasma volume expander and has an osmotic impact on the cerebral interstitium. There is proof that hypertonic saline has neurohumoral and vasoregulatory effects as well. In the context of vasospasm, it may also operate as a cerebral vasodilator.[21] With the administration of HTS, ICP reduction is safe to achieve. In those who have therapy-resistant rise of ICP, repeated bolus administration of HTS may result in a considerable reduction in ICP. A proper ICP reduction can prevent subsequent damage and potentially life-threatening consequences.[22] When utilized for patients with head injuries compounded by hemorrhagic shock, the benefit of improved survival was noted, leading to the initial recognition of HTS as a potentially more successful alternative for hemorrhagic shock resuscitation. HTS is typically administered as a bolus or continuous infusion at dosages of 1.0 to 4.0 mL/kg, with a concentration range of 3.0% to 23.4%.[23] The administration of HS needs to be taken into account, it may result in demyelination syndrome in patients with a chronic condition of hypernatremia and hyponatremia.[24] To prevent the negative effects, a periodic electrolyte serum check may be required. Because HS has a higher coefficient to cross the brain

barrier than mannitol, the rebound phenomenon is less frequent when administered with HS.[21]

Intracranial pressure monitoring

For most healthcare workers, including neurological surgeons and physicians, ICP is equivalent to a numerical figure. It might be the amount of fluid in an irrigation system or the value displayed on the display of the computer in millimeters of mercury (mmHg).[25] ICP is much more than just a number. To enhance clinical decision-making, a variety of ICP ratings and ICP-derived assessments have been investigated.[26] Normal mean ICP readings have not been determined since ICP assessments in individuals in good health cannot be justified ethically. Only indirect evidence concerning ICP from people who are "as normal as possible" is available. The aim, by TBI guidelines, is to keep mean ICP under 20 mmHg.[27] The mean ICP values don't seem to alter between the hours of day and night.[28] The average mean ICP values, on the other hand, are significantly dependent on body posture. The mean ICP decreases when a person stands up straight. reported that the positional variation in mean ICP might distinguish healthy persons from CSF disturbance patients. In our clinical practice, mean ICP in a standing position of less than 5 mmHg is considered abnormal.[29,30] To add clinical significance to mean ICP alone, it has been coupled with additional variables to form multiple indices. CPP, which is the variation between average arterial BP and average ICP (CPP = mean arterial BP-mean ICP), is probably the most well-known ICP-derived measure.[31] Other indicators employed in certain centers include the RAP, which stands for the relationship between amplitude and pressure, and the pressure reactivity index(PRx).[32] A RAP greater than 0.6 has been regarded as indicating a deteriorated pressure-volume reserve.[33] The PRx (moving association of average ICP and average arterial BP) is thought to be an indicator of auto-regulatory status or a measure of cerebrovascular responsiveness.[34]

Hyponatremia: an emergency in traumatic brain injury

The primary electrolyte imbalance seen in individuals with TBI is hyponatremia and is considered as most emergency, which is defined as serum sodium <135 meq/L. Hyponatremia has been documented to occur in 9.6% to 51% of TBI patients, and it is well-known that hyponatremia independently predicts a poor neurologic prognosis in TBI patients. The Syndrome of Inappropriate Antidiuretic Hormone Secretion (SIADH), hypopituitarism, Cerebral Salt Wasting Syndrome (CSW), and insufficient salt consumption in the diet are the major causes of hyponatremia in TBI patients.[35] Following traumatic brain injury, dysregulation of the neuroendocrine system is a common consequence (TBI). These hormone imbalances often have mild symptoms that are simple to overlook. Usually, hyponatremia is a sign of underlying illnesses that interfere with fluid homeostasis. Hyponatremia is a characteristic of the SIADH following brain injury in the majority of TBI patients, which is caused by pituitary failure. Hyponatremia linked to traumatic brain injury is often temporary and curable.[36] When mannitol is administered to reduce intracranial pressure in traumatic brain injury intravascular free water content is first raised, which might exacerbate electrolyte imbalances, such as hyponatremia. The second phase of action involves the excretion of mannitol in the urine together with an excess of free water, which may lead to hypernatremia because of the induced diuresis.[37] Mannitol also worsens the cerebral edema. It partially penetrates the vessel wall, despite its limited cross-sectional area, in individuals with cerebral hemorrhage, mannitol crosses the vascular wall more readily. Mannitol can penetrate the blood-brain barrier when taken fequently, which can exacerbate cerebral edema because the mannitol draws water into the brain rather than out of it. Mannitol treatment may cause patients' cerebral edema to deteriorate, particularly in children with cerebral hyperemia.[38] Hypertonic Saline Solution (HSS) restores intracranial compliance, extracts fluid from the interstitial space, and lowers intracranial pressure, mostly by preventing the buildup of extracellular osmolytes in the brain that is associated with blood-brain barrier malfunction.[39] For the treatment of increased ICP, mannitol remains the cornerstone of hyperosmolar therapy, however, a bolus infusion of HSS is more effective.[40] Thus in TBI patients without ICH, continuous HSS infusion enhanced Cerebral Perfusion Pressure (CPP), raised natremia and osmolarity, and reduced the likelihood of ICH.[41]

Comparison of hypertonic saline and mannitol

Intracranial pressure is a key indicator of decline in neurological function in patients with traumatic brain injury.[42] It has also been demonstrated that when cerebral perfusion pressure is severely low (50 mm Hg), intracranial pressure becomes an indicator of undesirable outcome, and maintaining intracranial pressure in the range of 18 to 23 mmHg verifies that cerebral perfusion pressure remains constant for a longer period.[43] Mannitol has been utilized for years to treat elevated intracranial pressure. Recommendations recently suggested that mannitol is more efficient than barbiturates in lowering intracranial pressure in people with traumatic brain injury.[44] Mannitol, causes a decrease in cerebral perfusion pressure due to its diuretic mechanism of action, which can cause the development of several adverse effects, including edema in the lungs, acute kidney dysfunction, and arterial hypotension, which causes a decrease in cerebral perfusion pressure due to its diuretic impact.[45] In a Randomised prospective trial conducted by Vialet *et al.*, the patients were randomly assigned to one of the two groups: one that received 7.5% hypertonic Saline (361 mOsm) and one that received 20% mannitol (175 mOsm) in the same amount (2 mL/kg). In comparison to hypertonic saline, the mannitol group had greater total and duration of daily periods of ICP > 25 mmHg and needed more CSF fluid drainage. This study also found that treatment failure was 70% higher in the mannitol group compared to 10% in the hypertonic saline group. There was no significant difference in mortality or neurological improvement after 90 days. It was noted that the study used both fluids with different osmolarities.[46] The optimum therapeutic agent for controlling intracranial pressure should reduce intracranial pressure while maintaining cerebral perfusion. Hypertonic saline boosts serum sodium and osmolality considerably. Excessive salt levels and osmolarity produce an overload of volume, edema of the lungs, and heart failure, or they might begin coagulopathy and hyperchloremic metabolic acidosis. Thus, hypertonic solutions should be administered with caution and under constant cardiac surveillance in individuals with impaired cardiac function.[47-48] In patients with head trauma (whether single or numerous injuries), it is important to avoid hypotension, since it boosts the incidence of mortality in this context.[49] In contrast to mannitol, an osmotic diuretic, HTS preserves and even improves the mean arterial blood pressure in various

kinds of shock.[50] Isotonic resuscitation using fluids in the trauma circumstance, necessitates a large amount of fluid, which can raise ICP. The significant benefit of HTS in this context is that blood pressure is maintained with minimal volume resuscitation, preventing possible iatrogenic ICP elevations.[51] Intravenous administration of hypertonic saline increased cerebral perfusion and shifted the oxygen dissociation curve, thus boosting the availability of oxygen and brain responsiveness while decreasing intracranial pressure and cerebral edema.[52] HTS may have a role in brain cell immune system regulation, perhaps leading to beneficial effects on inflammation and a better prognosis for TBI patients. The inflammatory cascade is activated by severe trauma, resulting in systemic allergic reaction syndrome. Furthermore, cerebral leukocytes move to wounded regions in response to TBI, resulting in peroxidase- and protease-mediated cell death.[53] The study conducted by Battison *et al*. in 2005 discovered that both mannitol and hypertonic saline considerably lowered ICP, however hypertonic saline dramatically reduced ICP more strongly and for an extended period than mannitol. The usage of the identical osmolarity between the two fluids is the study's key strength.[54] In the final analysis, mannitol is regarded as the "standard of care" treatment for TBI-induced intracranial hypertension because of its historical use rather than its efficacy against HTS. HTS offers numerous theoretical benefits over mannitol in terms of physiology. In clinical terms, HTS appears to be more effective than mannitol in lowering ICP, both in terms of degree and duration of decrease. Ultimately, HTS appears to promote brain tissue oxygenation more than mannitol. All of these benefits imply that HTS should be thoroughly researched so that it might potentially be utilized as an alternative to mannitol as a first-line treatment for the management of elevated ICP in TBI patients. It is uncertain if a bolus dosage or an infusion is required. The bolus dosage was administered at various proportions with no indication of superiority of any concentration in particular, although total osmolar load must be considered. Infusions with 3% HTS at a rate of 0.1-2mL/kg/h have been proven to be successful, with step-wise titration of the dosage to a goal of 145-155mEq/L NA+ (maximum 160mEq/L) and an osmolality of 320-330mOsm/L (maximum 360mEq/L). According to the literature, HTS infusion decreases ICP over 72 hours, however, this effect cannot be sustained with continued treatment. The bolus dosage can be administered alone or in conjunction with continuous infusion treatment. It is also used to reduce ICP in people who have not had surgery.[55] In the study conducted by De Vivo *et al.* the first group received mannitol, the following one received Mannitol+HTS, and the third group received solely HTS and the treatment continued for 72 hours, utilizing boluses three times each day. They concluded that HTS is a viable option for decreasing ICP in humans without affecting CVP or serum osmolality. It is unlikely to cause allergic responses or to transfer infectious agents, and it is readily managed by serum Na levels. In intracranial surgery, it is an acceptable substitution for mannitol.[56] Following elective craniotomy, mannitol, and HTS enhance CSF osmolality and are associated with comparable levels of cerebral relaxation, arteriovenous O_2 differential, and lactate. They propose that HTS should be employed instead of mannitol to reduce brain size in patients with and without subarachnoid hemorrhage, especially if they are hemodynamically unstable.[57] Resuscitation with fluids is crucial in TBI patients because it prevents hypotension and subsequent brain damage, both of which increase mortality. The Brain Trauma Foundation's care recommendations for TBI state unequivocally that hypotension must be avoided since it is an independent characteristic of poor prognosis. The administration of fluids in this patient, particularly with HTS alone or in combination with dextran, restores intravascular volume with less volume,[58] raises CPP, decreases ICP,[59] and regulates the inflammatory response.[60-67] The beneficial effect of HTS over mannitol in terms of potential long-term neurological consequences is still unknown. To solve this topic, a substantial prospective randomized investigation is required. Many of the issues have yet to be resolved, necessitating more studies to reach a firm judgment on the supremacy of these hyperosmolar drugs.

Evidence linking management of cerebral edema in traumatic brain injury

There have been few research that compare mannitol with HTS in the context of pure cerebral relaxation in tumors. De Vivo et al. undertook a prospective, randomized comparative analysis of supratentorial tumors. The study concluded that HTS is an efficient way to reduce ICP in people without affecting CVP or serum osmolality. It is unlikely to cause anaphylaxis or spread infectious agents, and serum Na levels can readily regulate it. It is a viable alternative to mannitol in intracranial surgery.[68] Several investigations have examined the cerebral effects of mannitol and HTS in patients with normal ICP. Gemma *et al.* found that HTS and mannitol produce acceptable cerebral relaxation in individuals undergoing elective craniotomy. This investigation was carried out using several neurosurgical techniques and non-equimolar dosages of HTS and mannitol.[69]

The clinical evidence comparing hypertonic saline and mannitol is discussed in the Supplementary Materials, Table 1.[70-77]

A summary of the comparison of safety efficacy profile of mannitol and hypertonic saline is available in the Supplementary materials, Table 2.

Conclusions

The significance of Intracranial Pressure (ICP) in managing conditions like traumatic head injuries and various neurologic diseases cannot be overstated. It is crucial to recognize that the primary objective of ICP management is to optimize cerebral perfusion pressure (CPP) for the preservation of cerebral metabolism and neurologic function. Solely concentrating on ICP, without considering other relevant physiologic variables such as CPP, oxygen utilization, and clinical outcomes, is a notable flaw in numerous published randomized controlled trials (RCTs) focusing on hyperosmolar therapy. Regardless of the specific hyperosmolar agent employed, the efficacy of hyperosmolar therapy for acute ICP management has been substantiated by both clinical experience and RCTs. Mannitol and HS are the most commonly used hyperosmolar agents, each with distinct physiologic properties affecting blood rheology, inflammation, neurochemistry, and hemodynamic regulation. While the idea of a universally applicable, single optimal agent is appealing, it is more plausible that different hyperosmolar agents may exert optimal therapeutic effects in diverse clinical contexts. For example, the relative merit of using HS, which expands systemic volume status, versus mannitol, which depletes it, needs exploration in patients with congestive heart failure experiencing elevated intracranial hypertension. Trials should consider testing equimolar agents infused over the same period to mitigate the effects of molarity and infusion time, a consideration often absent in existing literature. In conclusion, a thoughtful analysis of individual clinical scenarios, coupled with a rigorous interpretation

of existing literature, is essential for providing optimal patient care.

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Online supplementary material:

Table 1. Clinical evidence comparing hypertonic saline and mannitol.

Table 2. Summarising the comparison of safety efficacy profile of mannitol and hypertonic saline.