Comparative Study of 3 % Hypertonic Saline and Mannitol in the Management of Raised Intracranial Pressure: A Prospective Observational Study

Running Title: *Comparative Osmotherapy in Raised ICP*

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Abstract

Background: Raised intracranial pressure (ICP) is a common and life-threatening condition encountered in neurosurgical practice. Mannitol has been the traditional osmotic agent used, while hypertonic saline (HTS) has emerged as a promising alternative.

Objective: To compare the clinical outcomes, complications, and Glasgow Coma Scale (GCS) improvement in patients treated with hypertonic saline versus mannitol.

Materials and Methods: This prospective comparative study included 158 patients with traumatic brain injury, equally divided into two groups:

- Group A: 79 patients received 3% hypertonic saline
- Group B: 79 patients received 20% mannitol

Neurological outcome was assessed using Glasgow Coma Scale (GCS) improvement. Radiological outcome was assessed by reduction in midline shift on CT brain. ICU stay, complications, and mortality were analyzed.

Results: Mean GCS improvement was significantly higher in the hypertonic saline group (6.33 ± 2.33) compared to the mannitol group (5.88 ± 2.33) ($p < 0.05$). Reduction in midline shift was greater with hypertonic saline (5.15 mm vs 4.55 mm; $p < 0.05$). ICU stay was comparable ($p > 0.05$). Mortality was lower in the hypertonic saline group (6.3%) compared to the mannitol group (15.2%) ($p < 0.05$). Mannitol was associated with a higher incidence of acute kidney injury.

Conclusion: 3% hypertonic saline is superior to 20% mannitol in reducing cerebral edema and improving neurological outcome in head injury patients, with fewer complications and lower mortality.

Keywords: Raised intracranial pressure, Mannitol, Hypertonic saline, Glasgow Coma Scale

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Introduction

Raised intracranial pressure (ICP) is a serious and potentially life-threatening neurological condition that is commonly encountered in patients with traumatic brain injury, intracranial hemorrhage, brain tumors, and hydrocephalus. Prompt recognition and effective management are essential to prevent the development of secondary brain injury and to improve patient outcomes. [1,2] Elevated intracranial pressure can compromise cerebral perfusion and lead to progressive neurological deterioration if not treated appropriately.

Osmotherapy plays an important role in the management by improving cerebral perfusion pressure .[3,4] Among the available osmotic agents, mannitol has traditionally been the most widely used therapy for lowering intracranial pressure in neurosurgical practice. Its osmotic effect promotes the movement of water from the brain parenchyma into the intravascular compartment, thereby reducing intracranial volume and pressure.

However, despite its effectiveness, the use of mannitol may be associated with several limitations and adverse effects. Repeated administration can lead to significant diuresis, hypovolemia, electrolyte imbalance, and potential renal dysfunction.[5] These complications may negatively affect systemic hemodynamics and cerebral perfusion, particularly in critically ill patients.

In recent years, hypertonic saline has emerged as an alternative osmotic agent for the management of raised intracranial pressure. Hypertonic saline is generally well tolerated but may be associated with certain adverse effects. The most common is hypernatremia, which is usually mild and transient,

along with hyperchloremia and possible metabolic acidosis. Rapid correction of sodium can lead to osmotic demyelination syndrome (central pontine myelinolysis), a serious neurological complication. Cardiovascular effects include volume overload, hypertension, and risk of pulmonary edema, particularly in patients with compromised cardiac function. Local complications such as phlebitis may occur with peripheral administration. Although relatively safer than mannitol, careful monitoring of serum electrolytes and fluid status is essential to prevent complications. Hypertonic saline has been reported to produce a sustained reduction in intracranial pressure while maintaining intravascular volume and improving hemodynamic stability. [6] Because of these potential advantages, its role in the treatment of intracranial hypertension has been increasingly investigated.

The present study was therefore undertaken to compare the efficacy and safety of hypertonic saline and mannitol in patients with raised intracranial pressure.

Materials and Methods

Study Design and Setting

This prospective non-randomized observational comparative study was conducted for one year August 1, 2024 to July 31, 2025 in the Department of Neurosurgery at SRM Medical College Hospital and Research Centre, Potheri, Tamil Nadu. The study period included consecutive admissions of patients with raised intracranial pressure following traumatic brain injury who fulfilled the predefined inclusion and exclusion criteria.

Study Population

A total of 158 patients diagnosed with raised intracranial pressure based on clinical assessment and radiological findings were enrolled in the study. Raised intracranial pressure was identified by clinical features such as altered sensorium, pupillary abnormalities, and radiological evidence of cerebral edema or midline shift on computed tomography (CT) of the brain. Patients were equally divided into two treatment groups, with 79 patients in each group.

Inclusion and Exclusion Criteria

Patients with moderate to severe head injury and clinical and radiological evidence of raised intracranial pressure were included in the study. Patients were excluded if they had pre-existing renal failure, documented electrolyte imbalance at the time of admission, or pregnancy.

Treatment Groups

Patients were managed according to institutional protocols and assigned to one of two treatment groups based on the osmotic agent administered. Group A consisted of 79 patients who received 3% hypertonic saline, while Group B consisted of 79 patients who received 20% mannitol. Both groups received standard neurocritical care management in addition to osmotherapy, including airway protection, hemodynamic stabilization, and supportive care as per standard guidelines.

Outcome Measures

Neurological outcome was assessed using improvement in the Glasgow Coma Scale (GCS), calculated as the difference between admission GCS and post-treatment GCS (ΔGCS). Radiological outcome was evaluated by measuring the reduction in midline shift on follow-up CT brain imaging. Secondary outcome measures included duration of intensive care unit (ICU) stay, incidence of complications such as acute kidney injury and electrolyte disturbances, requirement for rescue osmotherapy, and in-hospital mortality.

Data Collection and Follow-up

Demographic details, clinical findings, radiological parameters, treatment details, and outcome variables were recorded prospectively using a structured data collection proforma. Patients were followed throughout their hospital stay, and outcomes were documented until discharge or death.

Statistical Analysis

Data were entered into Microsoft Excel and analyzed using appropriate statistical methods. Continuous variables were expressed as mean ± standard deviation (SD), while categorical variables were expressed as frequencies and percentages. Comparison of continuous variables between the two groups was performed using the Student's t-test, and categorical variables were compared using the Chi-square test. A p-value of less than 0.05 was considered statistically significant.

Results

A total of 158 patients with raised intracranial pressure following head injury were included in the study, with 79 patients allocated to the 3% hypertonic saline group (Group A) and 79 patients to the 20% mannitol group (Group B). The two groups were comparable with respect to baseline demographic characteristics, including age, sex distribution, and severity of head injury, with no statistically significant differences observed ($p > 0.05$) (Table 1).

Neurological Outcome

Neurological improvement was assessed using the change in Glasgow Coma Scale (ΔGCS) following osmotherapy. Both treatment groups demonstrated significant improvement in GCS scores. However, patients treated with 3% hypertonic saline showed a greater mean improvement in GCS (6.33 ± 2.33) compared to those treated with 20% mannitol (5.88 ± 2.25) (Figure 1). This difference was statistically significant ($p < 0.05$), indicating superior neurological recovery in the hypertonic saline group (Table 2).

Radiological Outcome

Radiological assessment using computed tomography of the brain demonstrated a

significantly greater reduction in midline shift in patients receiving hypertonic saline. The mean reduction in midline shift was 5.15 mm in the hypertonic saline group compared to 4.55 mm in the mannitol group as shown in figure 2, and this difference was statistically significant ($p < 0.05$). These findings suggest more effective reduction of cerebral edema with hypertonic saline.

Intensive Care Unit Stay

The duration of intensive care unit (ICU) stay was comparable between the two groups. The mean ICU stay was 23.95 days in the hypertonic saline group and 23.81 days in the mannitol group, with no statistically significant difference observed ($p > 0.05$).

Complications

The incidence of complications differed significantly between the two treatment groups. Acute kidney injury (AKI) was more frequently observed in the mannitol group, affecting 18 patients, compared to 8 patients in the hypertonic saline group ($p < 0.05$). Hypernatremia was observed in patients receiving hypertonic saline; however, it was mild and transient in nature and did not require discontinuation of therapy. The requirement for rescue osmotherapy was also higher in the mannitol group compared to the hypertonic saline group ($p < 0.05$).

Mortality

Overall mortality was significantly lower in the hypertonic saline group (Figure 3). Five patients (6.3%) in the hypertonic saline group succumbed during the hospital stay, compared to twelve patients (15.2%) in the mannitol group. This difference in mortality was statistically significant ($p < 0.05$).

Discussion:

Cerebral edema and raised intracranial pressure (ICP) continue to be important contributors to morbidity and mortality following traumatic brain injury (TBI) .[7,8] Effective osmotherapy is therefore essential to minimize secondary brain injury and improve neurological outcomes. Mannitol has long been regarded as the standard osmotic agent used in the treatment of raised ICP. However, in recent years, hypertonic saline has gained increasing attention as a potential alternative due to its favorable physiological effects .[9,10] The present study was undertaken to evaluate and compare the efficacy and safety of 3% hypertonic saline and 20% mannitol in reducing cerebral edema and improving neurological outcomes in patients with head injury.

While the primary injury occurs at the moment of trauma and is largely irreversible, secondary brain injury develops over time and may be preventable with appropriate management [11–14]. Raised ICP resulting from cerebral edema, alterations in cerebral blood flow, and impaired autoregulation plays a central role in the development of secondary brain injury [15,16]. Persistent raised intracranial pressure can reduce cerebral perfusion pressure, leading to cerebral ischemia, metabolic failure, and neuronal damage. Therefore, maintaining adequate ICP control is a cornerstone in the management of patients with traumatic brain injury [17–19] .

In the present study, a total of 158 patients with head injury were included, with 79 patients assigned to each treatment group. The choice between mannitol and 3% NaCl depends on the patient's clinical status. Mannitol was preferred in hemodynamically stable patients with normal renal function due to its rapid ICP-lowering effect but was avoided in hypotension or renal impairment because of diuresis. 3% NaCl was preferred in hypotensive, hypovolemic, or hyponatremic patients as it maintains intravascular volume and cerebral perfusion, but should be used cautiously in hypernatremia or cardiac failure. Neurological outcome was evaluated using improvement in the Glasgow Coma Scale (GCS), which remains a widely accepted and reliable indicator of neurological recovery in patients with traumatic brain injury. GCS continues to be a valuable tool in clinical practice because it is simple to use, reproducible, and correlates well with injury severity and patient prognosis. In your study, both mannitol and 3% NaCl were not given together routinely in the same patient. Each patient was assigned to one treatment group (either mannitol or hypertonic saline).

However, rescue osmotherapy was used in some cases—more commonly in the mannitol group—meaning that if initial treatment was insufficient, the other agent was added. So, both drugs may have been used in the same patient only as rescue therapy, not as standard simultaneous treatment.

In this study, the duration of administration of both 3% hypertonic saline and mannitol was not fixed and was individualized based on the patient's clinical condition. Osmotherapy was continued as needed according to neurological improvement, control of intracranial pressure, and radiological findings. The therapy was adjusted and tapered based on parameters such as serum sodium levels in the hypertonic saline group and renal function and serum osmolality in the mannitol group, rather than being given for a predefined duration.

Surgery was not a primary component—the study focused on conservative management of raised ICP with medical treatment.

Both treatment groups demonstrated improvement in neurological status following osmotherapy. However, patients treated with 3% hypertonic saline showed a higher mean improvement in GCS compared with those receiving 20% mannitol. Although the difference between the two groups was modest, even small improvements in GCS may have clinical significance in patients with head

injury, as they may reflect improved cerebral perfusion and reduced secondary brain damage.

The greater neurological improvement observed in the hypertonic saline group may be explained by its physiological characteristics. Hypertonic saline produces an osmotic gradient across the blood–brain barrier, promoting the movement of water from the intracellular and interstitial compartments of the brain into the intravascular space [20,21] . Unlike mannitol, which is rapidly redistributed and eliminated through osmotic diuresis, hypertonic saline tends to remain within the intravascular compartment for a longer duration, resulting in a more sustained reduction in cerebral edema [22,23]. Hyponatremia after administration of 3% NaCl is uncommon but can occur in certain situations. It may result from overcorrection followed by rebound dilution, especially if excess free water is administered or if there is ongoing sodium loss (e.g., SIADH or cerebral salt wasting). Inadequate dosing, interruption of hypertonic saline, or excessive intravenous fluids can also dilute serum sodium levels. Additionally, renal excretion of excess sodium after initial correction may contribute. Therefore, careful monitoring of serum sodium and fluid balance is essential to prevent both overcorrection and subsequent hyponatremia.

The improved neurological recovery seen in the hypertonic saline group may also be related to its ability to expand intravascular volume and maintain cerebral perfusion pressure without causing significant diuresis [24] .In contrast, mannitol acts mainly through osmotic diuresis, which may lead to intravascular volume depletion, hypotension, and electrolyte imbalance when administered repeatedly. These factors may adversely affect cerebral perfusion in patients with traumatic brain injury. Maintenance of adequate cerebral perfusion pressure is particularly important in these patients, as hypotension is known to be associated with poorer outcomes [25]. Higher mortality with mannitol is mainly related to its systemic side effects and hemodynamic impact. Mannitol causes osmotic diuresis, which can lead to hypovolemia, hypotension, and reduced cerebral perfusion pressure, especially with repeated doses. It is also associated with electrolyte imbalance and a higher incidence of acute kidney injury, as seen in your study. In addition, mannitol may cross a disrupted blood–brain barrier and accumulate in brain tissue, leading to rebound intracranial hypertension, which can worsen cerebral edema. These factors together can negatively affect neurological recovery and contribute to increased mortality compared to hypertonic saline.

In addition to its osmotic effects, hypertonic saline has been reported to improve cerebral microcirculation, reduce endothelial cell swelling, and modulate inflammatory responses [26,27]. These mechanisms may contribute to improved neuronal survival and better functional recovery. Mannitol, although effective in lowering ICP, may occasionally worsen cerebral edema in cases of blood–brain barrier disruption due to its potential accumulation within the brain tissue, which can lead to rebound intracranial hypertension [28] .

The complication profile observed in the present study also differed between the two treatment groups. Patients treated with mannitol experienced a higher incidence of complications, particularly acute kidney injury and electrolyte imbalance. In comparison, hypertonic saline was generally well tolerated. Although hypernatremia occurred in some patients receiving hypertonic saline, it was mild and transient and did not require discontinuation of therapy. These findings suggest that hypertonic saline may have a favorable safety profile in the management of raised ICP [29] .GCS improvement with 3% NaCl is generally earlier and more sustained, often beginning within 24–48 hours, due to better maintenance of intravascular volume and cerebral perfusion. In comparison, mannitol also produces early improvement but may be less sustained over time because of its diuretic effect, which can lead to hypovolemia and reduced cerebral perfusion. As observed in your study, the overall GCS improvement was greater with hypertonic saline than with mannitol, indicating better neurological recovery.

The findings of the present study are consistent with several previously published reports. Qureshi et al. demonstrated that hypertonic saline was effective in lowering intracranial pressure and maintaining cerebral perfusion pressure in patients with intracranial hypertension [30]. Similarly, Vialet et al. reported a more sustained reduction in ICP with hypertonic saline compared with mannitol in patients with severe traumatic brain injury [31] .These results highlight the potential advantage of hypertonic saline in the acute management of raised ICP.

However, some studies have reported similar efficacy between the two osmotic agents. Cottenceau et al. observed no significant difference in mortality between hypertonic saline and mannitol, although improved hemodynamic stability was noted with hypertonic saline [32] .Likewise, Sakellaridis et al. reported comparable ICP-lowering effects with both agents but noted fewer systemic complications with hypertonic saline [33]. The findings of the present study are in agreement with these observations and suggest that hypertonic saline may provide certain clinical advantages.

Unlike several previous studies that primarily focused on intracranial pressure measurements, the present study emphasized clinical neurological outcome. This approach enhances the clinical relevance of the findings, particularly in settings where invasive ICP monitoring may not be

routinely available. Clinical improvement reflected by changes in GCS remains an important and practical endpoint for evaluating treatment efficacy in patients with traumatic brain injury.

Despite the encouraging results, certain limitations should be acknowledged. The study was conducted at a single center, and long-term functional outcomes such as the Glasgow Outcome Scale or quality-of-life measures were not evaluated. In addition, invasive ICP monitoring was not uniformly performed in all patients, and outcome assessment relied largely on clinical parameters. Future multicenter randomized controlled trials with larger sample sizes, standardized ICP monitoring, and longer follow-up periods would help provide stronger evidence regarding the comparative effectiveness of these osmotic agents.

In summary, the present study demonstrates that 3% hypertonic saline is associated with greater neurological improvement compared with 20% mannitol, along with a lower incidence of complications. These findings support the growing role of hypertonic saline as a safe and effective osmotherapy option in the management of cerebral edema following traumatic brain injury.

Conclusion

Hypertonic saline is an effective and safe alternative to mannitol for the management of raised intracranial pressure with fewer complications

Declarations:

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Ethics approval and consent to participate: All procedures followed were in accordance with the ethical standards of the institutional ethical committee on human experimentation and in accordance with the Declaration of Helsinki. Informed consent was obtained from the participants.

Informed Consent: The authors obtained the appropriate consent from the patient for publication.

Conflict of interest: None declared.

Author Contribution: Manisha conceptualized the study, performed the clinical analysis, and drafted the manuscript. Dr.Mohamed Naleer H analyzed the data, critically revised the manuscript, and supervised the study. All authors read and approved the final version of the manuscript.

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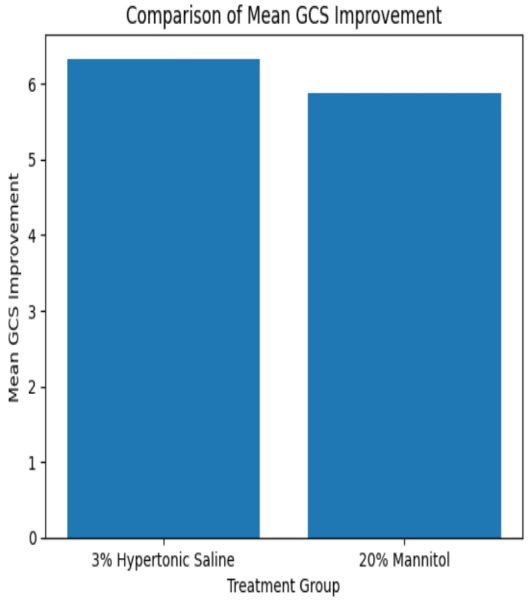
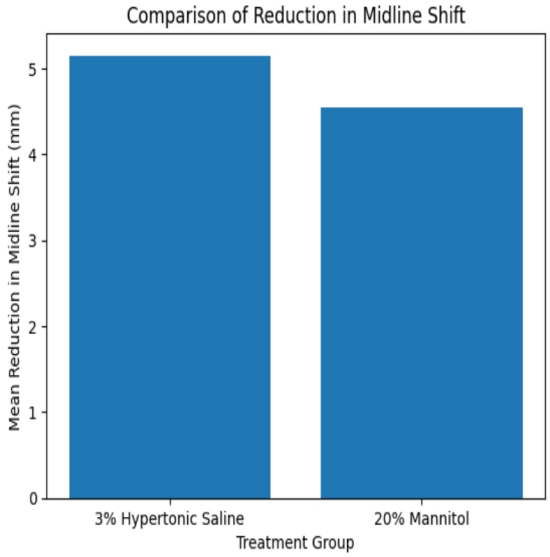
Figures:

Figure 1: Comparison of mean improvement in Glasgow Coma Scale (ΔGCS) between patients treated with 3% hypertonic saline and 20% mannitol.



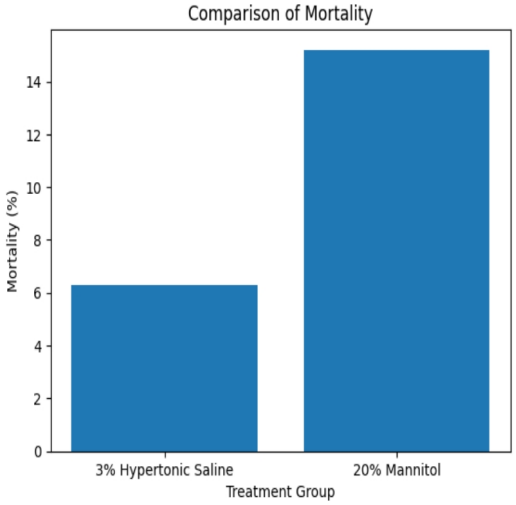
Bar diagram showing comparison of mean improvement in Glasgow Coma Scale (ΔGCS) between patients treated with 3% hypertonic saline and 20% mannitol. The hypertonic saline group showed a higher mean GCS improvement (6.33) compared to the mannitol group (5.88). The difference was statistically significant ($p < 0.05$).

Figure 2: Comparison of Reduction in Midline Shift



Bar diagram showing comparison of mean reduction in midline shift on CT brain between patients treated with 3% hypertonic saline and 20% mannitol. The hypertonic saline group demonstrated a greater mean reduction in midline shift (5.15 mm) compared to the mannitol group (4.55 mm). The difference was statistically significant ($p < 0.05$).

Figure 3: Comparison of Mortality



Bar diagram comparing mortality between patients treated with 3% hypertonic saline and 20% mannitol. Mortality was lower in the hypertonic saline group (6.3%) compared to the mannitol group (15.2%), and the difference was statistically significant ($p < 0.05$).

Tables:

Table 1: Comparison of Demographic Profile, Clinical Outcomes, Complications, and Mortality between Study Groups:

Parameter	3% Hypertonic Saline (n = 79)	20% Mannitol (n = 79)	p-value
Demographic Characteristics			
Mean age (years)	Comparable	Comparable	> 0.05
Sex distribution (M : F)	Comparable	Comparable	> 0.05
Severity of head injury	Comparable	Comparable	> 0.05
Neurological Outcome			
Mean GCS improvement (ΔGCS)	6.33	5.88	< 0.05
Radiological Outcome			
Mean reduction in midline shift (mm)	5.15	4.55	< 0.05
ICU Parameters			
Mean ICU stay (days)	23.95	23.81	> 0.05
Complications			
Acute kidney injury (number of patients)	8	18	< 0.05
Hypernatremia	Mild, transient	present	< 0.05
Need for rescue osmotherapy	Lower	Higher	< 0.05
Outcome			
Mortality	5 (6.3%)	12 (15.2%)	< 0.05

Table 2: Comparison of Mean ± Standard Deviation of Glasgow Coma Scale (ΔGCS) Improvement between Study Groups:

Group	n	Mean ± SD (ΔGCS)	p-value
3% Hypertonic Saline	79	6.33 ± 2.33	< 0.05
20% Mannitol	79	5.88 ± 2.25	< 0.05

Both groups had equal numbers of patients (n = 79). The mean improvement in GCS was higher in the 3% hypertonic saline group (6.33 ± 2.33) compared to the 20% mannitol group (5.88 ± 2.25). This difference was statistically significant ($p < 0.05$), indicating better neurological improvement with hypertonic saline.