SYSTEMATIC REVIEW

Efficacy of Intravenous 20% Mannitol vs 3% Hypertonic Saline in Reducing Intracranial Pressure in Nontraumatic Brain Injury: A Systematic Review and Meta-analysis

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Abstract

Background: Nontraumatic brain injury encompasses various pathological processes and medical conditions that result in brain dysfunction and neurological impairment without direct physical trauma. The study aimed to assess the efficacy of intravenous administration of 20% mannitol and 3% hypertonic saline to reduce intracranial pressure in nontraumatic brain injury.

Materials and methods: The Preferred Reporting Items for Systematic Reviews and Meta-Analysis guidelines were followed for study selection and data extraction. The search was conducted in the PubMed, Embase, and Scopus databases, including articles published in English from January 2003 to December 2023. Our study included randomized controlled trials, comparative studies, prospective analyses, and retrospective cohort studies. We extracted data on baseline characteristics of patients, intervention details, major outcomes, and complications. Quality assessment was performed using the Jadad scale and the Robvis assessment tool for risk of bias.

Results: A total of 14 studies involving 1,536 patients were included in the analysis. Seven studies reported hypertonic saline as more effective in reducing intracranial pressure, while three studies found similar effectiveness for both interventions. Adverse events were reported in only three studies. The studies that reported complication rates ranged from 21 to 79%. A meta-analysis was conducted on five studies, showing varying rates of adverse events associated with mannitol and hypertonic saline.

Conclusion: Both hypertonic saline solution and mannitol have been explored as treatment options for decreasing intracranial pressure in nontraumatic brain injuries. While some studies indicate the superiority of hypertonic saline, others report similar effectiveness between the two interventions.

Keywords: Administration, Brain injuries, Hypertonic, Hypertonic saline, Intravenous, Intracranial pressure, Mannitol, Meta-analysis, Retrospective studies.

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Highlights

A systematic review analyzed 14 studies on the efficacy of 20% mannitol and 3% hypertonic saline in reducing intracranial pressure in nontraumatic brain injury. Seven studies favored hypertonic saline, three found both interventions equally effective. Adverse events were reported in three studies, with rates ranging from 21 to 79%. Meta-analysis of five studies revealed varying rates of complications. Both treatments are explored, with some studies favoring hypertonic saline, while others suggest similar efficacy.

Introduction

A nontraumatic brain injury encompasses any form of brain damage or harm that does not result from an external force or physical trauma. This type of brain injury can occur for various reasons, such as stroke, infections, tumors, metabolic abnormalities, and neurological disorders.[1] Nontraumatic brain injury is a globally significant contributor to morbidity and mortality, often leading to enduring physical, cognitive, and emotional impairments that can persist over the long term.[2] Elevated intracranial pressure is a common complication of nontraumatic brain injuries and can lead to further brain damage if not managed promptly.[3] Therefore, prompt diagnosis and appropriate management of a nontraumatic brain injury are crucial to reducing the risk of complications and improving patient outcomes.[4]

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In nontraumatic brain injury cases, such as certain medical conditions or diseases, an increase in intracranial pressure can occur. This can happen due to conditions like brain tumors, hydrocephalus (excessive cerebrospinal fluid in the brain), or cerebral edema (swelling of the brain). Unlike traumatic brain injuries, where the impact directly affects the brain, non-TBI cases can involve indirect causes leading to elevated intracranial pressure. These causes might include infections like meningitis or encephalitis, strokes, brain abscesses, or other neurological disorders.[5] Intracranial hypertension refers to a medical condition characterized by

increased pressure inside the cranium. Typically, the pressure in the cranial cavity is measured in millimeters of mercury (mm Hg), and it should not exceed 20 mm Hg under normal circumstances. The adverse impacts of intracranial hypertension mainly stem from cerebral ischemia, which is a type of brain damage caused by reduced blood flow due to heightened intracranial pressure.[2] Due to its clinical manifestations, heightened intracranial pressure can be easily misdiagnosed as other conditions such as stroke, intoxication, post-ictal state, or infection.[5]

Therapeutic interventions play a crucial role in managing elevated intracranial pressure. One commonly used intervention is mannitol, a type of osmotic diuretic. Mannitol functions by elevating the osmolarity of the bloodstream, causing water to be drawn out of the brain tissue and consequently reducing brain volume. Mannitol is a highly effective intervention for the management of acute intracranial pressure, as it rapidly decreases intracranial pressure and enhances cerebral perfusion pressure.[6] Typically, it is administered as an initial bolus dose, followed by a continuous infusion. However, mannitol may have some adverse effects, such as dehydration, electrolyte imbalance, and renal dysfunction. Therefore, it is essential to monitor the patient's hydration status, electrolyte levels, and renal function during mannitol therapy. While mannitol is widely acknowledged for its effectiveness, certain studies have indicated that hypertonic saline solutions might be more efficacious in reducing intracranial pressure compared to mannitol.[7,8] The recommended dose for mannitol administration is usually between 0.25 and 1.0 gm/kg of body weight, and the commonly used concentration is 20%.[9]

Hypertonic saline is a solution with a higher concentration of sodium than normal saline (0.9% NaCl). It is a promising alternative to mannitol for reducing intracranial pressure in patients with neurologic conditions.[10] Hypertonic saline works by osmotically drawing water out of the brain tissue, thereby reducing brain volume and intracranial pressure.[11] Certain studies have demonstrated that hypertonic saline solutions are more effective than mannitol in lowering intracranial pressure, particularly in patients with traumatic brain injury or subarachnoid hemorrhage. The hypertonic saline solution concentration typically ranges from 3 to 23.4% NaCl, and the infusion rate is usually slow and controlled to prevent hypernatremia and other adverse effects.[12] Hypertonic saline may also improve cerebral blood flow and oxygenation, thereby improving neurological outcomes. Nevertheless, additional studies are necessary to establish the long-term safety and effectiveness of hypertonic saline solutions as compared to mannitol.[11]

One of the theoretical advantages of hypertonic saline over mannitol is its potential to have lower permeability across the blood-brain barrier.[13] This is due to its higher reflection coefficient, which means that it may be less able to penetrate the brain tissue and cause osmotic shifts that could potentially worsen brain injury. However, further studies are needed to confirm this potential benefit and determine its clinical significance. This systematic review and meta-analysis is aimed at comparing 20% mannitol and 3% hypertonic saline for their effectiveness in decreasing intracranial pressure in nontraumatic brain injuries.

Materials and Methods

Study Design

The study will adhere to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PICOS) framework, incorporating the following elements: Population (P): The study focused on patients with nontraumatic brain injuries of any etiology. Intervention (I) and Comparator (C): The study compared the effectiveness of hypertonic saline with 20% mannitol in reducing intracranial pressure. Outcomes (O): The primary outcome was to determine whether hypertonic saline demonstrates superiority over mannitol in reducing intracranial pressure among patients with nontraumatic brain injuries. Study Design (S): The study encompasses randomized controlled trials, prospective studies, comparative studies, clinical trials, and retrospective cohort studies. By utilizing the PICOS framework, the study aimed to systematically assess and analyze the available evidence to evaluate the relative effectiveness of hypertonic saline and mannitol in decreasing intracranial pressure among patients with nontraumatic brain injury.

Search Databases and Search Strings Used

For this study, we searched databases such as Cochrane Review, PubMed, Embase, and Scopus. We limited our search to only articles published in English in the last 20 years, from January 2003 to December 2023. Our search strategy combined medical subject headings (MESH) and text words relating to nontraumatic brain injury, stroke, raised intracranial pressure, hypertonic saline, and mannitol. We used Boolean operators such as "AND," "OR," and "NOT" to combine our search terms. We also performed a manual search of the references to the identified articles to ensure their completeness. The search strategy was designed to identify relevant studies that evaluate the effectiveness of hypertonic saline and mannitol in reducing intracranial pressure in patients with nontraumatic brain injuries as well as their safety.

Inclusion and Exclusion Criteria

We included (1) studies involving patients aged ≥18 years; (2) studies involving patients with nontraumatic brain injury, including all causes of raised intracranial pressure except traumatic brain injury; (3) studies published in English; and (4) studies published in the last 20 years, between January 2003 and December 2023. *In vitro* and *in vivo* studies, case reports of a single patient, systematic reviews and meta-analyses, review articles, studies on patients ages <18 years and studies that were not published in English were excluded from the analysis. Figure 1 shows the PRISMA flowchart of the study.

Data Extraction

Following the initial screening, two reviewers conducted a thorough reading of the selected literature that meets the inclusion criteria. If any disagreements arise, a third reviewer is consulted for further evaluation. The essential and relevant data, including article type, primary author's name, publication year, sample size, age, and gender distribution, intervention details such as mannitol and saline concentrations, primary and secondary outcomes, complications, and limitations of each study, were systematically extracted and recorded.

Literature Quality and Risk of Bias Assessment

The studies included in the analysis were subjected to a quality evaluation using two assessment tools: the Jadad scale (about the GRADE system) and the Robvis' (ROB 2.0) assessment tool for risk of bias. Two researchers evaluated each included study independently using the Jadad scale, which assigns scores based on quality, and the GRADE scoring system to provide a qualitative assessment of the studies. Any disagreements that arose were resolved by a third researcher. In addition, the risk of bias in each study was assessed by Robivis' assessment tool, with discrepancies discussed by the two researchers to ensure accuracy.

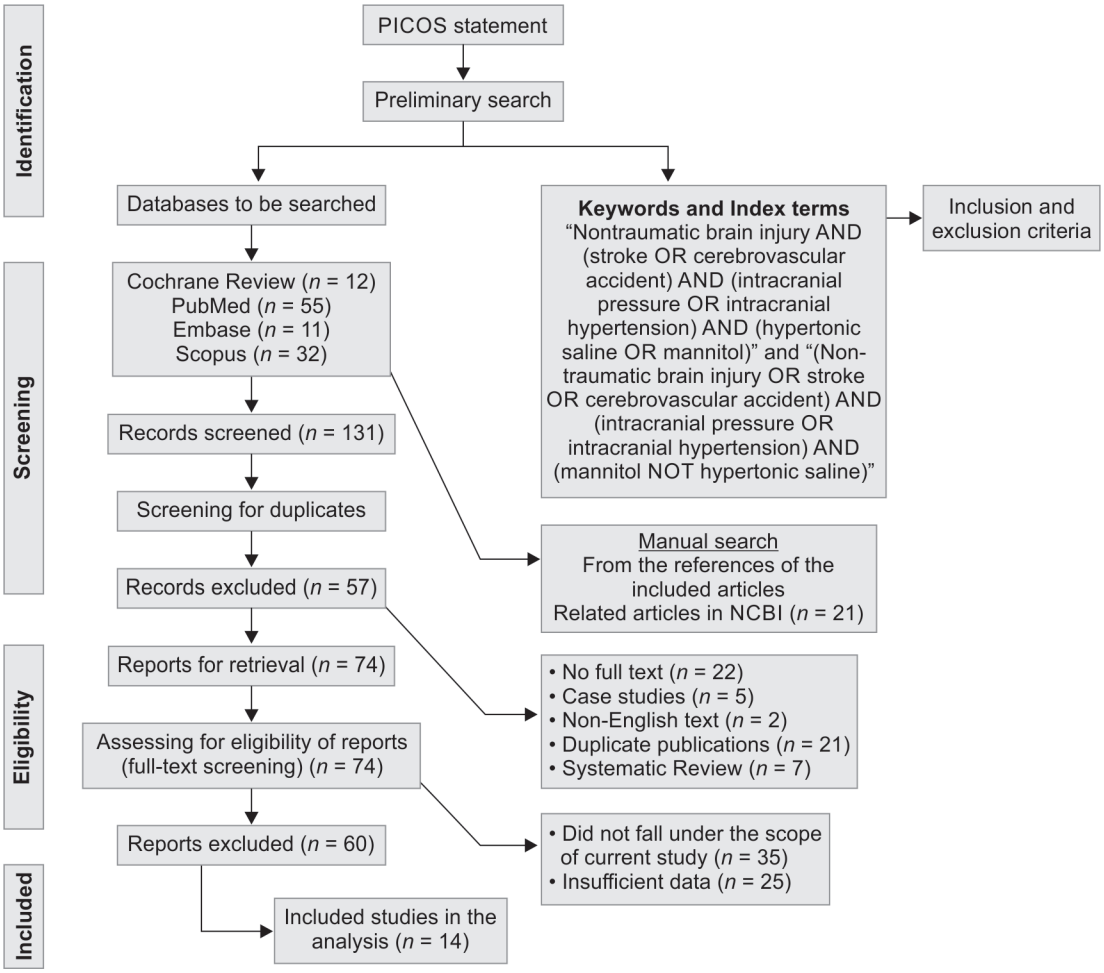

Fig. 1: PRISMA chart of the study design

Meta-analysis of Data

The statistical analysis was conducted using RevMan version 5.4. The weighted mean difference, or standardized mean deviation, will be calculated to determine the size of the effect. We performed a meta-analysis using the effect sizes calculated. A forest plot generated in Microsoft Excel will be used to calculate the odds ratio (OR) for higher efficiency or success rates, with a 95% confidence interval (CI) used for interval estimation.

Results

Literature Selection

On initial screening, a total of 131 articles were retrieved from three main databases (PubMed, Embase, and Scopus). After screening for duplications, non-English articles, and articles without full text, we excluded case studies, duplicate publications, systematic reviews and meta-analyses, narrative reviews, and duplicate publications, which left us with a total of 74 articles. After excluding 60 articles as they did not fall under our scope and lacked sufficient data, we included a total of 14 studies in our analysis.

Characteristics of the Included Studies

The study included 14 articles, which included five randomized controlled trials, three clinical studies, four retrospective studies, one prospective study, and one comparative analysis. The year of publication ranged between 2003 and 2021. Our analysis included a total of 1,536 patients who were diagnosed with increased intracranial pressure (>20 mm Hg) due to various clinical conditions. Three studies did not report the gender distribution, which corresponds to 234 participants, whereas the remaining 11 studies comprise 751 males and 551 females in total. The age of the patients in the included studies varied between 2 and 75 years. Detailed baseline characteristics of the patients are provided in Table 1.[7,8,14–25]

Clinical Conditions Causing Nontraumatic Brain Injuries

Among the 14 studies, one did not specify the clinical conditions that contributed to nontraumatic brain injury in the patients, and one study mentioned acute brain injury as its cause.[14,25] However, among the remaining 12 studies, cerebral edema and intracerebral hemorrhage contributed to nontraumatic brain injury in 46% ($n = 6$); stroke was reported in 23% ($n = 3$); and the aneurysm was reported in 15% ($n = 2$) studies.

Invention and Outcomes

The mannitol and hypertonic saline solution concentrations are provided in Table 2.[7,8,14–25] The commonly used concentrations of mannitol and hypertonic saline solution were 20% and 7.5%, respectively. Out of the 14 included studies, seven reported that

hypertonic saline solution is superior to mannitol in decreasing intracranial blood pressure, whereas three studies reported that both mannitol and hypertonic saline solution are similarly effective.[7,8,14,17–20,22,23,25] Table 3 presents the detailed primary and secondary outcomes of the studies included in our analysis,[7,8,14–25] and Table 4 shows the data extraction of the included studies.[7,8,14–25]

Table 1: Baseline characteristics of the patients in the included studies

Study	Sample size	Mean age (years)	Gender distribution	
			Male	Female
Yildizdas et al.[7]	67	Mannitol, 67.9 ± 46.4; HSS, 68.4 ± 50.3; HSS + mannitol, 70.5± 52.2 (months)	31	36
Harutjunyan et al.[8]	32	47 ± 16	17	15
Vialet et al.[14]	20	Mannitol, 30.8 ± 19; HSS, 35.0 ± 18	9	11
Bereczki et al.[15]	805	66 ± 12.5	471	334
Larive et al.[16]	28	46 (18–20)	18	10
Battison et al.[17]	9	>15	NR	NR
Francony et al.[18]	20	Mannitol, 43 ±11; HSS, 37 ± 16	16	4
Upadhyay et al.[19]	200	2–18	NR	NR
Hauer et al.[20]	215	HSS, 58.7 ± 13.3; non-HSS, 62.8 ± 13.0	124	91
Helbok et al.[21]	12	44 (39–54)	5	7
Huang and Yang[22]	25	53.7 ± 13.5	NR	NR
Sharma et al.[23]	31	HSS group, 45.25 ± 11.67; Mannitol group, 48 ± 15.03	13	18
Aminmansour et al.[24]	41	62.5 ± 8.4	30	11
Tatro et al.[25]	31	29	17	14

HSS, hypertonic saline solution; NR, not reported

Literature Quality and Risk of Bias Assessment

Table 5 shows the quality of the included studies based on the Jadad scale scores and the quality of the studies based on the GRADE system.[7,8,14–25] Four out of 14 studies were of moderate quality; two studies showed low quality, and the remaining eight studies showed high quality. Figures 2 and 3 show the variables included in the risk of bias assessment plot and summary, respectively.

Meta-analysis

Only five studies were subjected to meta-analysis, which included an analysis of the adverse events. Eight studies were excluded as there were no details reported on adverse events or due to incomplete data on complications. The studies that reported complication rates ranged from 21 to 79% with OR (95% CI) values of 21 (2.7–67.8), 0.6 (0.3–0.8), 0.04 (0.003–0.109), 1.7 (0.2–3.7), and 1.7 (0.7–3.9).[6,7,14–16] Figure 4 shows the forest plot constructed to represent the rate of adverse events associated with mannitol and hypertonic saline solution treatments for nontraumatic brain injury. Figure 5 shows the forest plot of the effectiveness and favorable outcomes of hypertonic saline solution over mannitol.

Discussion

Nontraumatic brain injury refers to a diverse range of conditions that lead to brain dysfunction and neurological impairment in the absence of direct physical trauma. Unlike traumatic brain injury, which is caused by an external force striking the head, nontraumatic brain injury refers to a variety of pathological processes, medical illnesses, and diseases that can cause brain damage.[26] Out of the 14 studies included in the analysis, the nature of the studies were randomized controlled trials, clinical, retrospective, comparative, and prospective studies. The nature of the study, the direction of the research, and the patient selection were diverse among the

Table 2: Intervention details of the included studies

Study	Clinical condition	ICP (mm Hg)	Intervention details	
			Mannitol	Hypertonic saline
Yildizdas et al.[7]	Cerebral edema	>20	20% (0.25–0.5 gm/kg)	3% (155–165 mEq/L)
Harutjunyan et al.[8]	Cerebral edema; ischemic stroke	>20	15%	7.2%
Vialet et al.[14]	NR	>20	20%	7.5%
Bereczki et al.[15]	Acute stroke	>20	NR	NA
Larive et al.[16]	Cerebral edema	>20	1–30%	2–3%
Battison et al.[17]	Subarachnoid hemorrhage; refractory intracranial hypertension	>20	20%	7.5%
Francony et al.[18]	Stroke	>20	20% (osmolarity, 1100 mOsm/L)	7.45% (osmolarity, 2548 mOsm/L)
Upadhyay et al.[19]	Cerebral edema	>20	20%	3%
Hauer et al.[20]	Severe intracerebral bleeding, acute ischemic stroke, aneurysmal subarachnoid bleeding	>20	NA	3%
Helbok et al.[21]	Nontraumatic, severe acute hemorrhagic stroke	>20	20% (1 gm/kg) (495 ± 109 mOsm)	NA
Huang and Yang[22]	Aneurysmal subarachnoid hemorrhage	>20	20%	3%
Sharma et al.[23]	Aneurysm	NR	20%	3%
Aminmansour et al.[24]	Nontraumatic intracerebral hemorrhage	NR	20%	NA
Tatro et al.[25]	Acute brain injury	>20	0.5 gm/kg	23.4% (30 mL)

NA, not applicable; NR, not reported

Table 3: Outcomes of the study

Study	*Primary outcomes*	*Secondary outcomes*	*Interpretation*
Yildizdas et al.[7]	HSS treatment proves to be highly effective and safe for infectious, anoxic, hemorrhagic, and metabolic conditions.		HSS demonstrates superior effectiveness over mannitol.
Harutjunyan et al.[8]	HSS is superior to mannitol in decreasing increased ICP.	7.2% HSS at 1.4 mL/kg is effective and safe.	HSS demonstrates greater effectiveness than mannitol in managing increased ICP.
Vialet et al.[14]	HSS demonstrates greater effectiveness compared to mannitol.	NR	HSS has been identified as a viable and secure primary intervention for managing elevated ICP in individuals who have sustained head injuries and require osmotherapy.
Bereczki et al.[15]	No significant progress has been reported.	NR	Mannitol may be a recommended option for acute stroke; however, further investigation is required.
Larive et al.[16]	The hypernatremia target was reached in 14 patients (74%), with 7 of them achieving hypernatremia within the first 24 hours.	Mean ICP, 16.6 ± 10.9 mm Hg; mean CPP, 89.3 ± 18.8 mm Hg	The medical team must exert intensive efforts to rapidly achieve and maintain a hypernatremic state when using HTS for cerebral edema.
Battison et al.[17]	HSS exhibits a significant reduction in ICP compared to mannitol.	The duration of effect for HSS was longer compared to mannitol.	When administered via an equimolar, rapid intravenous infusion, HSS proves to be more efficient than mannitol in reducing ICP.
Francony et al.[18]	ICP reduction: Mannitol group, by 45 ± 19%; HSS group, by 35 ± 14%.	Mannitol potentially improves blood rheology, thereby exerting additional effects on brain circulation.	In patients with brain injury, a solitary infusion of 20% mannitol at equimolar concentration is as efficacious as a 7.45% HSS solution infusion in mitigating ICP.
Upadhyay et al.[19]	During the initial 12 hours, 3% HSS displayed greater efficacy than mannitol, and later it remained equally or more effective.	There was a highly significant decrease in coma hours with mannitol administration.	3% hypertonic saline can safely replace mannitol in cerebral edema treatment.
Hauer et al.[20]	ICP levels decreased with the administration of HSS.	There was a significant decrease in the in-hospital mortality rate. (17.0% in the HSS-treated group vs 29.6% in the non-HSS group).	Hypertonic saline given early and consistently to severe cerebrovascular illness patients at risk of intracranial hypertension is safe. This method may also reduce ICP crises and deaths.
Helbok et al.[21]	In 80% of mannitol administrations, ICP dropped below 20 mm Hg, but within 4 hours, it increased above 20 mm Hg in 52% of cases.	CPP has been successfully restored.	Mannitol effectively reduces ICP and restores CPP.
Huang and Yang[22]	Both 3% HSS and 20% mannitol rapidly reduced ICP in patients with nontraumatic brain injuries caused by aneurysmal subarachnoid hemorrhage.	After treatment with HSS and mannitol, the plasma osmolality initially increased and then decreased.	3% HSS should be considered the first-line osmotic drug for decreasing ICP in patients with nontraumatic brain injuries caused by aneurysms.
Sharma et al.[23]	The brain relaxation achieved with HSS was equivalent to that with mannitol.	Mannitol resulted in higher urine output, while HSS led to higher serum sodium levels.	Both mannitol and HSS exhibit similar effectiveness in reducing ICP.
Aminmansour et al.[24]	Preintervention, the ICH volume was 22.1 ± 6.3 mL, whereas post-intervention, it increased to 38.4 ± 19.3 mL.	61% of patients experienced increased hemorrhage and ICH, accompanied by a decline in GCS and Hounsfield value; 9.8% showed improvement; and 29.3% had no change in their clinical conditions.	Mannitol injections did not effectively reduce hemorrhage size.
Tatro et al.[25]	The absolute reduction in ICP at 30, 60, and 120 minutes after hyperosmolar drug infusion and the time to the next elevated ICP did not differ.		HSS and mannitol demonstrated comparable effectiveness.

CPP, cerebral perfusion pressure; HSS, hypertonic saline solution; ICH, intracerebral hemorrhage; ICP, intracranial pressure; NR, not reported

Table 4: Data extraction from the included studies

Study	*Study type*	*Objectives*	*Interpretation*	*Limitation*	*Complications*
Yildizdas et al.[7]	Retrospective study	The HSS and mannitol were compared against each other in decreasing ICP due to cerebral edema.	HSS demonstrates superior effectiveness over mannitol.	Hyperchloremic metabolic acidosis	NR
Harutjunyan et al.[8]	RCT	A comparison of effectiveness and safety of HSS vs mannitol for decreasing ICP was performed.	HSS demonstrates greater effectiveness than mannitol in managing increased ICP.	Small sample size.	NR
Vialet et al.[14]	RCT	The clinical advantages of augmenting the osmotic load in hypertonic solutions utilized for managing episodes of refractory intracranial hypertension in patients with severe head injuries were evaluated.	HSS has been identified as a viable and secure primary intervention for elevated ICP in individuals with head trauma who require osmotherapy.	NR	NR
Bereczki et al.[15]	Clinical trial	The effectiveness of mannitol in reducing ICP was evaluated.	Mannitol may be a recommended option for acute stroke; however, further investigation is required.	HSS was not used in the control group.	At one year, the mannitol group had a 38% case fatality rate, while the nontreated group had a 25% case fatality rate.
Larive et al.[16]	Clinical study	The HSS and mannitol were compared against each other in decreasing ICP.	The medical team must exert intensive efforts to rapidly achieve and maintain a hypernatremic state when using HTS for cerebral edema.	No control group was used.	NR
Battison et al.[17]	RCT	The HSS and mannitol were compared against each other in decreasing ICP.	When administered via an equimolar, rapid intravenous infusion, HSS proves to be more efficient than mannitol in reducing ICP.	NR	NR
Francony et al.[18]	RCT	In terms of reducing ICP, HSS and mannitol were evaluated.	In patients with brain damage, a single equimolar infusion of 20% mannitol is as efficacious as a 7.45% HSS infusion in lowering ICP.	These findings cannot be applied to patients who had critically low CPP or $PbrO_2$ levels at the outset.	NR
Upadhyay et al.[19]	Prospective randomized study	The effectiveness and side effects of 3% HSS and mannitol in treating children with increased ICP were evaluated.	In the treatment of cerebral edema, 3% hypertonic saline is a safe and effective alternative to mannitol.	None reported.	NR
Hauer et al.[20]	Retrospective analysis	To study the safety and effects of an early continuous infusion of hypertonic saline in patients with cerebral edema and underlying cerebrovascular disease.	In patients with severe cerebrovascular illness and impending intracranial hypertension, early and continuous infusion of hypertonic saline is safe and may lower the frequency of ICP crises and fatality rates.	Pilot nature of the study.	There was cardiac arrhythmia, heart, liver, or renal failure, as well as pulmonary edema.
Helbok et al.[21]	Retrospective study	To examine whether mannitol treatment for elevated ICP improves brain metabolism alongside the expected decrease in ICP.	Mannitol effectively reduces ICP and restores CPP.	No control group was used; the sample size was smaller.	NR

(Contd...)

Table 4: *(Contd...)*

Study	*Study type*	*Objectives*	*Interpretation*	*Limitation*	*Complications*
Huang and Yang[22]	Comparative study	The efficacy of HSS vs 20% mannitol in the treatment of elevated ICP was assessed.	3% HSS should be considered the first-line osmotic medication in the treatment of intracranial hypertension in patients with aneurysmal subarachnoid hemorrhage.	NR	Death, survival in a vegetative state, severe disability, and needing care in daily life
Sharma et al.[23]	RCT	The effects of equiosmolar and equivolemic 3% HSS and 20% mannitol on cerebral relaxation were evaluated.	Mannitol and HSS show similar efficacy in decreasing ICP.	Much shorter follow-up period (48 hours).	HSS group had increase serum sodium (returned to normal within 24 hours).
Aminmansour et al.[24]	Clinical trial study	To determine the impact of 20% mannitol on the outcome of patients with nontraumatic intracerebral hemorrhage.	Mannitol injections did not effectively reduce hemorrhage size.	No control group was used.	NR
Tatro et al.[25]	Retrospective cohort study	The absolute drop in ICP after 60 minutes following infusions of 23.4% sodium chloride against mannitol was evaluated.	HSS and mannitol demonstrated comparable effectiveness.	NR	NR

CPP, cerebral perfusion pressure; HSS, hypertonic saline solution; ICP, intracranial pressure; NR, not reported; RCT, randomized controlled trial

Table 5: Quality assessment of the included studies

Name of the study	*Selection bias*	*Performance bias*	*Reporting bias*	*Attribution bias*	*Other bias*	*Results*	*Quality of the study (GRADE scoring)*
Yildizdas et al.[7]	1	1	1	1	1	5	High
Harutjunyan et al.[8]	1	1	1	1	1	5	High
Vialet et al.[14]	1	1	1	1	0	4	Moderate
Bereczki et al.[15]	0	1	1	1	1	4	Moderate
Larive et al.[16]	0	1	1	1	1	4	Moderate
Battison et al.[17]	1	1	1	1	1	5	High
Francony et al.[18]	1	1	1	1	1	5	High
Upadhyay et al.[19]	1	1	1	1	1	5	High
Hauer et al.[20]	1	1	1	1	0	4	Moderate
Helbok et al.[21]	0	1	1	1	1	4	High
Huang and Yang[22]	1	1	1	1	1	5	High
Sharma et al.[23]	1	1	1	1	1	5	High
Aminmansour et al.[24]	0	1	1	1	0	3	Low
Tatro et al.[25]	1	0	0	1	1	3	Low

Selection bias, Has the study included comparisons between groups or existing data?; Performance bias, Has the study reported the estimated effects clearly?; Reporting bias, Was the study free from problems with measurements or classification of outcomes?; Attribution bias, Has the study reported complete outcome data?; Other Bias, Was the study free from limitations?; Jadad Scale Score, "0–3": Low quality; "4": Moderate quality; "5": High quality

included studies. The majority of the patients were males, and the highly susceptible age was around 45 years. In the treatment and management of elevated intracranial pressure induced by nontraumatic head injuries, we examined the effects of 20% mannitol vs 7.5% hypertonic saline solution.

Nontraumatic brain injury can arise from a multitude of factors, including cerebrovascular accidents (e.g., strokes), infections, metabolic disorders, anoxic brain injury, neoplastic growths, neurodegenerative diseases, and autoimmune conditions affecting the central nervous system. Each underlying cause of a nontraumatic brain injury presents unique challenges in diagnosis, treatment, and long-term care, necessitating a comprehensive understanding of the associated mechanisms and clinical manifestations. In our analysis, most studies reported nontraumatic brain injury due to cerebral edema and intracerebral hemorrhage, followed by stroke and aneurysm.

For many years, mannitol has been employed to decrease elevated intracranial pressure. Recent research indicates that mannitol is more effective than barbiturates in lowering intracranial pressure in individuals with traumatic brain injury, and it is recommended by guidelines.[27] Mannitol, on the other hand, has its own set of limitations, as it can cause acute renal failure, pulmonary edema, exacerbation, and rebound of pre-existing cerebral edema (due to its accumulation in brain tissue via a

compromised blood-brain barrier caused by trauma), and arterial hypotension, which results in a decrease in cerebral perfusion pressure due to its diuretic properties.[28] However, in our analysis, only three out of 14 included studies reported adverse events like increased fatality, cardiac arrhythmia, heart, liver, or renal failure, or pulmonary edema.[15,20,22]

In a study conducted by Shi et al.,[10] it was found that the use of 3% hypertonic saline resulted in a significant increase in serum sodium and osmolality. These elevated levels of sodium and osmolarity can have adverse effects, such as excessive fluid accumulation leading to heart failure and pulmonary edema. Additionally, they may also contribute to the development of hyperchloremic metabolic acidosis and coagulopathy.[29] But we have observed similar results in only one study; however, the elevated serum sodium was reported to return to normal within a day.[23]

The interpretation of the primary outcomes varied across the studies. Hypertonic saline solution has been demonstrated to have more efficacy than mannitol in several studies, while others found no significant improvement or similar effectiveness between the two interventions. Secondary outcomes included factors such as duration of effect, improvements in coma hours, reduction in mortality rate, restoration of cerebral perfusion pressure, and changes in intracranial hemorrhage volume. The studies presented valuable findings regarding the efficacy and safety of hypertonic saline and mannitol in the management of intracranial pressure in patients with nontraumatic brain injuries. These investigations shed light on the potential benefits and risks associated with the use of these therapies for reducing intracranial pressure in such patients.

Based on our analysis, our main findings were: (1) 7.5% hypertonic saline solution is superior to 20% mannitol in decreasing intracranial pressure; (2) males were more frequently affected than females with increased intracranial pressure; and (3) both 20% mannitol and 7.5% hypertonic saline solution are similar in terms of complications; no serious adverse events have been reported in either of the medications, so they may be regarded as highly safe and effective.

Our study has a few limitations. It is important to note that this analysis is based on the selected studies and their reported outcomes. The included studies varied in their study designs, sample sizes, and methodologies, which may introduce heterogeneity and potential biases. Although eight out of 14 studies were of high quality, we could not entirely rule out the possibility of publication bias.

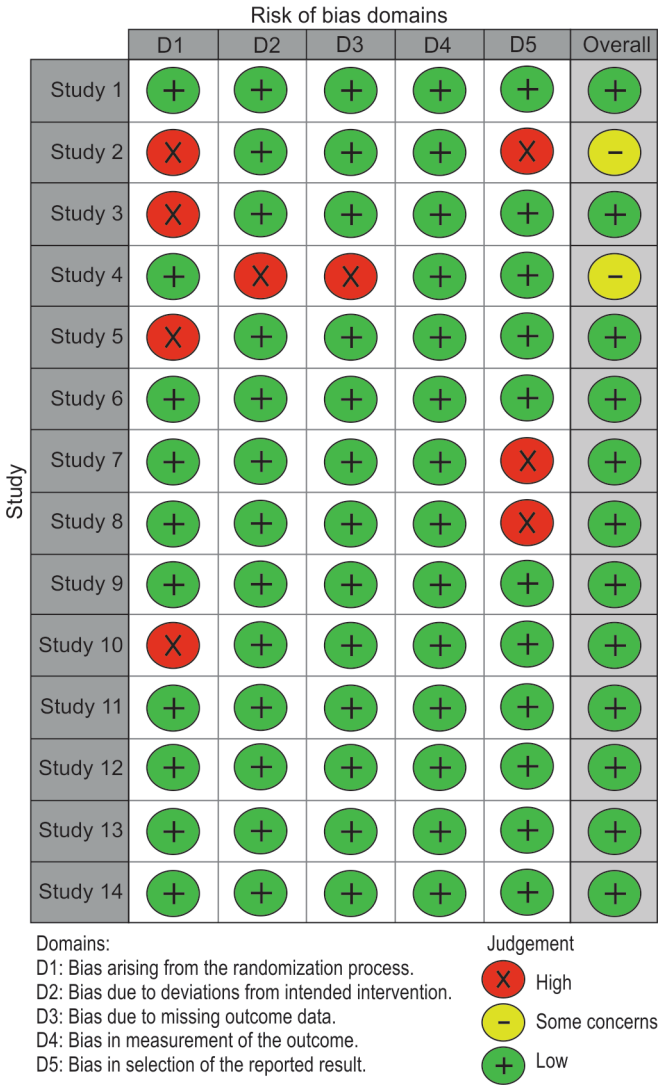

Fig. 2: Risk of bias assessment

Conclusion

In conclusion, the available evidence suggests that both hypertonic saline solution and mannitol have been explored as treatment options for decreasing increased intracranial pressure in patients with nontraumatic brain injuries. While some studies indicate the superiority of hypertonic saline solutions over mannitol, others report similar effectiveness between the two interventions. To establish more definitive evidence and inform clinical decision-making in the management of elevated intracranial pressure, further research is required, specifically well-designed randomized controlled trials. These trials would contribute to a more robust understanding of the effectiveness and safety of

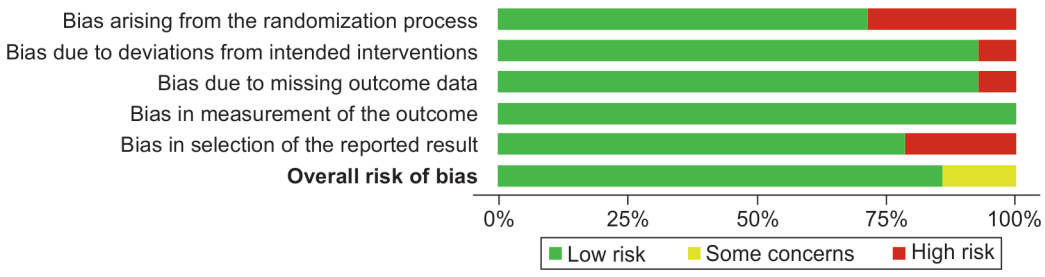

Fig. 3: Risk of bias assessment–Summary plot

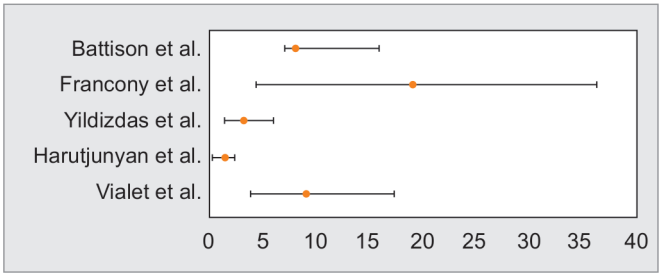

Fig. 4: Forest plot for the adverse events

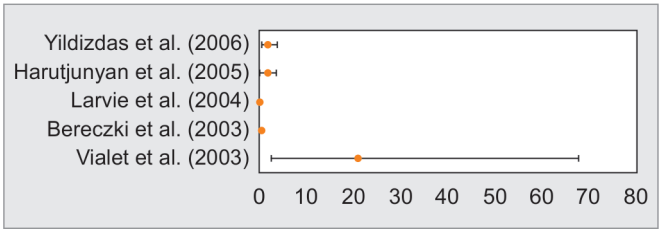

Fig. 5: Forest plot showing the effectiveness of HSS over mannitol

different interventions, including hypertonic saline and mannitol, in addressing increased intracranial pressure. Such studies would provide clinicians with more reliable guidelines for treating patients with this condition.

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