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HYPERTONIC SALINE FOR ISCHEMIC STROKE: A REVIEW

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ABSTRACT

Background and objective:
Elevated intracranial pressure (ICP) is a critical complication of ischemic stroke. This review article summarizes existing literature pertaining to the role of hypertonic saline (HTS) in lowering ICP in ischemic stroke patients.

Methods:
Studies were selected using a comprehensive search of several research databases. Studies conducted in adult (aged 18 and older) human patients receiving HTS osmotherapy for elevated ICP were included, encompassing a wide range of neurological conditions and various administration methods, durations, and concentrations of HTS.

Results:
We found HTS to reduce ICP in ischemic stroke patients, on par effectively, and in some studies, superior to more conventional ICP-lowering methods such as mannitol. Patients with comorbid conditions such as cerebrovascular and renal diseases also tolerated HTS well. The risk of developing hypernatremia was significantly higher in patients receiving HTS osmotherapy. Neurological complications, such as central pontine myelinosis, were not observed in any of the participants; however, no clear benefit regarding the long-term neurologic outcome of these patients has been reported thus far.

Conclusion:
While encouraging, existing literature on the use of HTS as a treatment for elevated ICP still needs to be more conclusive and necessitates further research. Questions regarding duration, optimal concentration of intervention, and method of administration need to be addressed by future randomized controlled trials.

Keywords: Ischemic stroke, Cerebral edema, Intracranial hypertension, Osmotherapy, Hypertonic saline

INTRODUCTION

Stroke is the second leading cause of mortality worldwide and is associated with high morbidity.[1] It can further be classified into two categories: ischemic and hemorrhagic, with the former accounting for nearly 80% of the cases.[2] Malignant or massive strokes cause severe cerebral edema, resulting in brain tissue shifting and herniation. These account for less than 10% of all ischemic strokes.[3] Cerebral edema formation causes a subsequent rise in intracranial pressure (ICP), eventually leading to secondary neuronal damage.[4] Considering the disease burden, it is of immense public health importance to explore different options for the acute management of ischemic stroke. Several medical therapies have been proposed to manage cerebral edema and elevated ICP. These include but are not limited to, osmotherapeutics, barbiturates, and hyperventilation.[5]

Mannitol is A commonly used treatment option for cerebral edema. However, it has become increasingly uncommon due to significant adverse effects on cessation, such as electrolyte imbalances, acute kidney injury, and rebound intracranial hypertension. Hence, its role as the standard treatment has diminished.[6] Barbiturates are said to work by decreasing cerebral metabolism but are not the mainstay therapy due to their significant adverse effects and very short-acting benefits. Similarly, hyperventilation is also not recommended in such patients due to the extensive adverse effects profile. Moreover, newer, more effective treatments with fewer side effects have emerged.[5]

One such treatment is hypertonic saline (HTS). A significant body of research concludes that HTS is comparable to or even better than mannitol for the reduction of ICP, especially when it comes to ICP refractory to mannitol.[7] Despite its widespread use, no set guideline currently dictates our use of HTS. Furthermore, there needs to be more data regarding its safety and efficacy. This narrative review aims to provide insight into the efficacy, mode of action, and potential side effects of HTS for ischemic stroke to better equip clinicians with the right tools to care for their patients.

Osmolarity & BBB

The blood-brain barrier (BBB) acts as a highly selective and partially permeable boundary that prevents the entry of circulating blood components into the extracellular fluid of the central nervous system.[8] It comprises the cerebral capillaries' endothelial cells, astrocytes, and pericytes buried within the capillary basement membrane.[9,10] Several factors, such as the size of the substance and its lipid solubility, affect the substance's permeability across the BBB. This specialized mechanism allows the selective diffusion of small molecules while actively transporting essential nutrients, ions, and large molecules crucial for neural function. Water molecules can also efficiently diffuse across the BBB, which helps maintain appropriate osmotic balance.[11]

Osmolarity refers to the concentration of osmotically active particles per unit volume of a solution, indicating its osmotic pressure. This measurement is crucial for determining water and solute movement through semipermeable membranes, such as the blood-brain barrier.[12] The blood-brain barrier's selective transport is influenced by the osmotic effectiveness or tonicity of particles, which depends on the barrier's permeability restrictions.[13]

Mechanism of raised ICP

Complications such as ischemic injury, hemorrhage, or lesions can lead to cerebral edema. Cerebral edema in the aftermath of an ischemic stroke can be classified as cytotoxic, ionic, or vasogenic. Initially, cytotoxic edema occurs due to the failure of Na/K ATPase pumps, causing intracellular Na and fluid build-up. This is followed by ionic and vasogenic edema caused by disrupting the blood-brain barrier.[4] This can cause increased ICP, ultimately leading to poor neurological outcomes and mortality.[14] The Monro-Kellie hypothesis explains that ICP depends on tissues, blood, and CSF contained by the rigid skull, where a decrease in one factor compensates for an increase in another.[15] However, when compensatory mechanisms are exhausted, ICP dramatically rises, potentially causing mass effect and brain matter herniation.[12]

Mode of action (MOA) of hypertonic saline in ICP reduction

Hypertonic saline exerts its effect mainly by two mechanisms: by forcing a shift in fluid from inside the cells to the capillary lumen. This effect greatly depends on the osmotic gradient established.

HTS is commonly used to treat acute brain injuries, such as ischemic stroke, intracranial hemorrhage, and traumatic brain injury, as it effectively reduces ICP and hemispheric edema. Many studies have highlighted the neuroprotective properties of HTS in decreasing mortality after cerebral ischemia.[16,17] Studies have shown that HTS can reduce the size of the infarct and brain water content. It is accomplished by suppressing the secretion of neuroinflammatory mediators such as TNF-α and IL-1β in activated microglia, both in vivo and in vitro. The suppression is achieved through the notch signaling, which works in synergy with the NF-κB pathway.[18] HTS has a higher solute concentration than the surrounding tissues. Therefore, it forces fluid out of the cells, bringing down cerebral edema.[19]

Recently, the role of HTS has increased as a substitute for mannitol to regulate brain edema. HTS is proposed to be a favorable osmotic agent as sodium chloride is entirely barred from an intact BBB. Moreover, HTS expands the intravascular volume with rising mean arterial blood pressure, improving cerebral perfusion pressure (CPP). An animal study found that infusion of 7.5% HTS, initiated six or 24 hours after ischemia induction, significantly decreased water content in both hemispheres. Beneficial results were reported after a continuous infusion lasting one to four days. The serum osmolality exceeded 350 mOsm/L during this time. However, reducing the saline concentration (to 3%) did not affect the infarct volume or the water content of the ischemic brain regions.[5]

METHODS

Eligibility Criteria

We included randomized controlled trials (RCTs) and retrospective chart reviews (RCRs) assessing the efficacy of Intracranial pressure (ICP) osmotherapy on pertinent clinical and functional outcomes in patients with ischemic stroke. Specific criteria for

comparison groups were not imposed, and studies without them were also included. Our primary outcome was changes in intracranial pressure (ICP) secondary to HTS osmotherapy. Our secondary outcome was functional outcome.

We only searched for literature in the English language. We excluded trials that were conducted on animal subjects or pediatric patients under 18 years of age. Reviews, systematic reviews, meta-analyses, and prospective cohort studies were not considered. We only included articles published between 1950 and 2022.

Information Sources

The following electronic databases were consulted: Medline via PubMed, the Cochrane Library, Web of Science, ClinicalTrials.gov, and Scopus. Data was managed through Rayyan online services. These databases were last consulted in August 2023.

Search Strategy

A search string was engineered with a combination of MeSH terms including "osmotherapy", "hypertonic saline", "hypertonic sodium chloride" "brain edema", cerebral edema", "intracranial hypertension", "ischemic stroke", and keywords relating to the topic to identify all RCTs and RCRs in which HTS was used in the management of ischemic stroke.

Selection Process and Data Extraction

Literature obtained from electronic databases was screened for duplicates. We extracted the following data from each study: its design, number of total participants, number of ischemic stroke patients, dosage and duration of HTS intervention, control/comparative group, functional outcome, and limitations.

EXISTING LITERATURE ON HTS AND STROKE

Retrospective chart reviews

When analyzing 76 transtentorial herniation (TTH) events among 68 patients, out of which eight had a stroke, Koenig et al. concluded that even though outcomes of TTH were poor, treatment with HTS was associated with a rapid reduction in TTH and ICP in three-fourths of the patients.[20] However, despite the successful reversal, outcomes remained poor. This cohort tolerated HTS well and did not report any cases of central pontine myelinolysis. They did report a fall in hemoglobin and a rise in bilirubin in two patients. Despite no established causal relationship, the absence of any alternate explanation raises questions.

Froelich et al. did a retrospective chart analysis of prospectively collected data and found no association between continuous HTS and increased risk of renal failure, infection, or deep vein thrombosis. They did report a significant risk of developing moderate (Na >155 mmol/L) and severe (Na >160 mmol/L) hypernatremia. Therefore, continuous HTS was deemed safe in severely injured patients, given that sodium levels are monitored carefully.[21]

A 2013 study evaluated the safety and efficacy of 14.6% or 23.4% HTS for refractory intracranial hypertension. None of the 55 patients enrolled in the study experienced central pontine myelinolysis. Repeat doses were efficacious enough to reduce ICP, with a mean reduction of 49.5% after each dose. Furthermore, efficacy was comparable among the two groups.[22]

Chris Carter et al. compared the safety of and efficacy in reducing intracranial hypertension of 5% NaCl with 23.5% NaCl among 44 patients with elevated ICP (>20 mm Hg). They reported comparable median percentage reductions in ICP between the two groups up to 120 minutes. Time to administration was also compared, with the 5% NaCl group reporting a shorter median time. Central line placement resulted in delays in administration in two patients in the group receiving 23.5% NaCl. No difference was seen in the prevalence of adverse effects in both cases.[23]

Anunit J.S. Chugh et al. compared patients with malignant ischemic infarcts managed with continuous HTS with those managed with routine medical care. Baseline clinical and radiographic parameters were comparable in both cohorts, and no significant difference was observed between the rate and timing of surgery, complications, and mortality. They concluded that there was no improvement in clinical outcomes or significant benefit of using continuous HTS. A small sample size limited the study, and due to its retrospective nature, the radiographic and clinical evaluation period needed to be standardized.[24]

Studies on patients with various conditions

In a retrospective analysis by Hauer et al. early continuous HTS infusion was studied for safety and

effects in patients with cerebral edema and underlying cerebrovascular disease. The infusion was continued until there were no signs of intracranial hypertension or edema exacerbation in brain image and clinical course. They concluded that a continuous HTS infusion is safe, and there are no signs of neurological worsening. Clinicians were advised to strictly monitor patients and avoid concurrent use of piperacillin/tazobactam to prevent severe hypernatremia.[16]

Hirsh et al. did a retrospective study using 23.4% saline in patients with renal failure undergoing renal replacement therapy. They observed that patients with renal failure tolerated 23.4% saline well, and hypotension was the most common side effect.[25] As seen previously, despite the successful reversal of TTH, outcomes remained poor.[6]

Corry et al. did a retrospective and prospective review. Admission diagnosis, creatinine changes, and HTS formulations (3% NaCl, 3% NaCl/sodium acetate mix, and 23.4% NaCl) were compared. The comparison group consisted of patients receiving only lactated ringers or normal saline. They reported no correlation between saline type and renal function. It was concluded that changes in sodium and chloride levels may have a negative impact on renal function. Therefore, the use of HTS should be carefully considered. The authors proposed that the reduced renal blood flow may be due to prior use of medications, such as angiotensin-converting enzyme inhibitors, in the context of rapid fluctuations in Na and Cl.[26]

Erdman et al. did a multicenter, retrospective study of patients receiving continuous HTS infusions. Out of 337 patients included, 33.5% had an ischemic stroke. AKI was reported in 54 patients, with 28 classified as AKIN stage 1, and the remaining 26 were divided between AKIN classes 2 & 3. Patients developing AKI were likelier to receive loop diuretics, hypertonic intravenous fluids, piperacillin/tazobactam, and mannitol. They were also more likely to have longer ICU stays and a history of chronic kidney disease (CKD). [27]

Randomized control trials

Stefan Schwarz et al. investigated the effects of HTS on stroke patients. Six of the eight patients had an ischemic stroke. They had 22 episodes of increased ICP that did not respond to treatment with 20% mannitol. Successful results were observed within 10 minutes of infusion, with the highest ICP decrease noted as 9.9 mm Hg at 35 minutes post-infusion. However, subsequently, there was a rise in ICP. At the end of the study, four patients died of uncontrollable intracranial hypertension, and the remaining were severely disabled. There was no mean arterial blood pressure change, although the cerebral perfusion pressure remained elevated.[28]

Gilles Francony et al. conducted a study to compare the effects of equimolar doses of 20% mannitol solution and 7.45% HTS in treating 20 patients with continuous elevated ICP of >20 mm Hg due to traumatic brain injury or stroke. Only one of the 20 patients had an ischemic stroke. The study found that the mannitol group showed a 45% reduction in ICP from baseline values, while the HTS group showed a 35% reduction after 60 minutes of infusion. Furthermore, mannitol increased cerebral perfusion pressure and diastolic and mean blood flow velocities.[29]

In a study by Michael N. Diringer and his colleagues, the impact of 20% mannitol and 23.4% saline infusion on cerebral blood flow, oxygen metabolism, oxygen extraction fraction, and blood volume was evaluated. Nine patients with ischemic stroke and large hemispheric infarction were involved in the study. However, neither treatment group showed significant changes in the infarct core, peri-infarct, or ipsilateral regions. In both treatment groups, arterial pCO2, arterial oxygen content, blood pressure, renal function, and temperature remained stable. Although a trend for increased CBF was noted in the contralateral hemisphere after mannitol infusion, it was not statistically significant. During the study period, a strong association was observed between the percentage change in CBF in the contralateral and non-ischemic hemispheres post-osmotic therapy and the mean blood pressure.[30]

Yingying Su et al. compared the efficacy and safety of employing 10% HTS and 20% mannitol for treating increased ICP in patients with large hemispheric infarction (LHI). Forty-nine episodes of ICP ≥15mmHg were seen among 14 study participants. Similar efficacy was seen in the reduction of ICP to baseline in both treatment groups, and no notable differences were observed in either the duration or degr reduction. While HTS treatment resulted in better ICP reduction for most time points, the group treated with mannitol experienced a more pronounced drop in MAP. On the other hand, the HTS group showed a more significant

rise in CPP.[31]

HTS vs. mannitol

In another study, the incidence of adverse effects in 19 consecutive patients treated with 2-3% HTS admitted to the neurosciences critical care unit were compared to a contemporary cohort of patients receiving mannitol as the sole form of osmotherapy. Although an association was observed between increased pneumonia risk and HTS, there was no notable contrast in adverse effects between the two cohorts.[32]

Side effects

Despite the potential benefits of hypertonic saline, it is crucial to consider the adverse effects associated with its use in stroke patients. Numerous studies have reported several complications related to HTS administration, such as pulmonary edema, diabetes insipidus, hyperchloremia, cardiac arrhythmias, hypotension, coagulopathy, hemolysis, and acute kidney injury (AKI). [25,27]

Systemic effects

Prolonged use of HTS in stroke patients with hypernatremia increased the risk of elevated blood urea nitrogen (BUN) and serum creatinine (Cr). Erdman et al. reported that 16% of neurocritical care patients receiving continuous infusion of HTS developed acute kidney injury (AKI), associated with significantly prolonged ICU stays and increased mortality (48.1% vs. 21.9%). Patients with AKI were more likely to have severe hypernatremia, hyperchloremia, and hyperosmolality compared to those without AKI (46.3% vs. 19%, 79.6% vs. 55.1%, and 51.9% vs. 18.9%, respectively). Furthermore, concurrent use of piperacillin/tazobactam in HTS patients raised AKI risk by 290%. Other risk factors included a history of chronic kidney disease, severe hypernatremia, male gender, and the African American race.[27]

Carter et al., when comparing the use of 5% NaCl with 23.4% NaCl found that both groups had a similar prevalence of adverse events, which was 27%. The adverse effects were mostly the same between the groups, except for a slightly higher incidence of pleural effusions in the 5% NaCl group (75% vs 32%). 23 Hauer et al. observed a similar prevalence of adverse effects in a study comparing early continuous HTS infusion to a historical control group with underlying cerebrovascular disease. Adverse effects included cardiac arrhythmias, acute renal, liver, or heart failure, and pulmonary edema, with no significant differences between the groups.[16]

Froelich et al. reported that continuous 3% HTS as maintenance fluid in brain injury patients significantly increased the incidence of moderate and severe hypernatremia compared to normal saline. The mortality rate was 41%, and hypernatremia was considered a contributing factor to mortality in 16% of the patients. 21 Additionally, Larive et al. established no significant difference in the prevalence of adverse effects in HTS and mannitol cohorts. Adverse effects observed in the HTS cohort included pneumonia (26.3%), bacteremia (15.8%), dysrhythmia (5.3%), hypokalemia (31.6%), and hyponatremia after HTS discontinuation (5.3%). One patient in the HTS group who received propofol was noted to have both heart block and bacteremia during the HTS infusion. They did not report any cases of acute renal failure in either group. [32]

Neurological effects

Central pontine myelinolysis, though an often-feared complication, was not observed in any participants.[33] It has been observed that continuous HTS therapy may lead to a paradoxical increase in radiographic cerebral edema. In later stages of ischemic strokes, hyperosmolar substances leak into the extravascular compartments due to blood-brain barrier breakdown. This can be the reason for the observed effects. Administering HTS in a transient or bolus manner can be more effective, as it relies on vascular osmolality and autoregulation to induce neuronal dehydration. A continuous infusion of hypertonic saline can be detrimental, particularly during late-stage ischemic stroke.[24] Moreover, to prevent the risk of rebound edema, HTS should ideally be gradually tapered, and the serum sodium level should be kept at least 10–12 mEq/L over 24 hours. [34]

Table 1 and Table 2 summarize the various studies considered in this review.

Table 1: Summary of clinical human studies using Hypertonic Saline in adult patients with Ischemic Stroke

Author/year	Study type RCT/ case control, chart review	Diagnosis Ischemic stroke/ non-traumatic ICH/other	Number of patients	Intervention HTS (concentration), mannitol, both	Duration Hours/ days	Outcome measure Mortality/ ICP/ other	Conclusion Beneficial/ no benefit/ worsening/ inconclusive	Limitations
Koenig et al. 2008 (20)	Retrospective cohort	Non-traumatic ICH, meningitis, subarachnoid hemorrhage, subdural hematoma, epidural hematoma	68	23.4% saline (30 to 60mL)	30 to 60 mL bolus infusion	Clinical reversal of TTH in 75% of cases and decrease in ICP.	Prompt reversal of transtentorial herniation and decreased intracranial pressure. More infrequent side effects.	Retrospective design. No control group.
Froelich et al. 2009 (21)	Retrospective analysis of prospectively collected data	Ischemic stroke, traumatic brain injury, or subarachnoid hemorrhage	187	2/3% HTS	3% or 2% Continuous HTS infusion at a rate of 1.5mL/kg/bw for at least 24 hours	Increased risk of hypernatremia noted with the use of HTS. No increase in the rate of infections, renal dysfunction, or DVT was seen.	Continuous HTS administration is safe if sodium levels are carefully monitored.	Mortality rates were not reported as patients were transferred. Cut-off values based on previous literature. Retrospective design.
Lewandowski-Belfer et al. 2013 (22)	Retrospective review	Ischemic stroke, non-traumatic ICH, subarachnoid hemorrhage, meningitis, vertebral artery dissection	55	24 or 48 mL of 14.6% HTS or 15 or 30 mL of 23.4% HTS	Intravenous bolus infusion over 20 min	The mean reduction of 49.5% ICP after each dose.	Beneficial and safe as a treatment option for refractory intracranial hypertension.	Retrospective design, no control group, interpatient variability in dosing.
Chris Carter et al. 2017 (23)	Single-center, retrospective, case-control	Traumatic brain injury, ischemic stroke, non-traumatic ICH	44	5% NaCl vs. 23.4% NaCl	Bolus infusion over 15 minutes	Both groups have similar efficacy at lowering ICP if given at equimolar Doses.	Similar efficacy at lowering ICP if given at equimolar doses. Similar prevalence of adverse effects. 5% NaCl has a decreased time to administration.	Retrospective design, Relatively small sample size.
Anunit J.S. Chugh et al. 2021 (24)	ischemic stroke	43	2 or 3% HTS	Bolus followed by continuous infusion for 24 hours	Baseline clinical and radiographic parameters were similar. No change was reported between rates and timing of decompressive surgery, mortality, and complications. Increased change in midline shift in the HTS group.	No advantage seen with the use of continuous HTS. May have caused worsening of cerebral edema.	Limited sample size, retrospective study design.	Ischemic stroke
Hauer et al. 2011 (16)	Retrospective	Ischemic stroke, Aneurysmal subarachnoid hemorrhage, ICH	100	3% HTS	Continuous infusion over 13 days	Decreased episodes of increased ICP in patients, a significant reduction in hospital mortality.	Early and continuous infusion of HTS is safe and might decrease the mortality rate and frequency of ICP crises.	Pilot character, comparison to historical control group, heterogenous patient collective with three different cerebrovascular diseases.
Hirsh et al. 2012 (25)	Retrospective cohort	Stroke, ICH, subdural hematoma	254	23.4% saline and/or mannitol	30 mL HTS bolus given over 5–10 min 1–2 g/kg/dose mannitol	Clinical reversal of TTH and reduction in ICP.	Safe and beneficial in patients with renal failure.	Small sample size, retrospective study design, no control group.
Corry et al. 2014 (26)	Retrospective review	Ischemic stroke, traumatic brain injury, ICH, subarachnoid hemorrhage	1329	3% NaCl, 3% NaCl/sodium acetate mix, and 23.4% NaCl	IV Infusion	Stroke patients showed weak correlations between the increase in Cr and the rise in Na and Cl.	Cr directly correlates with Na^+ or Cl^- in stroke, Na^+ in TBI, and Cl^- in other populations.	Retrospective design and single-center location.
Erdman et al. 2016 (27)	Multicenter, retrospective	Ischemic stroke, traumatic brain injury, ICH	337	3% HTS	Continuous infusion for median time: 49 hours 4 min	Past medical history of CKD, serum Na>155mmol/L, concomitant administration of piperacillin/tazobactam, African American race, and male gender are independent predictors of AKI in these patients.	AKI is commonly reported in patients receiving continuous HTS and may significantly affect clinical outcomes.	Retrospective study design. No control group.

Table 2: Summary of Randomised Controlled Trials using Hypertonic Saline in adult patients with Ischemic Stroke

Author/year	Study type RCT/ case-control, chart review	Diagnosis Ischemic stroke/ non-traumatic ICH/other	Number of patients	Intervention HTS(concentration), mannitol, both	Duration Hours/ days	Outcome measure Mortality/ ICP/ other	Conclusion Beneficial/ no benefit/ worsening/ inconclusive	Limitations
Stefan Schwarz et al. 2002 (28)	Prospective case series	Hemorrhagic stroke, ICH	8	75 mL of 10% HTS	Infusion over 15 minutes	Decrease in ICP in first 10 minutes in all episodes.	HTS effectively reduces ICP and increases cerebral perfusion pressure after mannitol failure.	Small sample size
Gilles Francony et al. 2008 (29)	Parallel, randomized	Traumatic brain injury, non-traumatic ICH, ischemic stroke	20	45% hypertonic	Infusion over 20 minutes	Reduction of ICP by 35% in the HTS group and 45% in the mannitol group.	The two treatments were equally effective in reducing ICP for patients with brain injuries.	Stroke, traumatic brain injury and intracerebral hematoma patients were grouped. FVm values were used to estimate cerebral autoregulation status. Only patients with CPP of >60 mm Hg were included. Only 1 out of 20 patients had ischemic stroke.
Michael N. Diringer et al. 2010 (30)	Randomised trial	Ischemic stroke	9	20% mannitol and 23.4% saline infusion (intermittent bolus infusion)	1.0 g/kg of mannitol or 0.686 ml/kg of saline infused over 15 min	Increase in CBF in the contralateral hemisphere after mannitol infusion.	At higher perfusion pressures, osmotic agents may cause a rise in CBF in non-ischemic tissue.	Small sample size. Time course of the cerebrovascular response to osmotic agents was not studied.
Yingying Su et al. 2020 (31)	Prospective self-crossover	Large hemispheric infarction	14	10% HTS and 20% mannitol (infusion)	400 ml/h mannitol, 130 ml/h HTS	Similar efficacy was seen in the reduction of ICP to baseline in both treatment groups.	Both can potentially be used as first-line agents in the treatment of intracranial hypertension caused by LHI.	Small sample size. No conclusion regarding long-term side effects and outcomes can be drawn.

CONCLUSION

The mechanism of action of hypertonic saline in reducing ICP is still unclear. Existing literature shows that HTS effectively reduces ICP in various diseases, including, but not limited to, ischemic stroke. It is crucial to emphasize that HTS is also the treatment of choice for treating cases of raised ICP refractory to hyperventilation and mannitol. Patients with co-morbidities like cerebrovascular and renal disease were able to tolerate HTS, which was more effective in lowering ICP than mannitol. Both continuous and bolus infusions and different concentrations have been used in different settings, with neither superior to the other. The potential for osmotic demyelination syndrome is the most concerning complication associated with HTS therapy, although it was not observed in any of the studies analyzed.

RECOMMENDATIONS FOR FURTHER RESEARCH

Despite the extensive research conducted on HTS therapy, there still needs to be more conclusive evidence to dictate guidelines. There are essential questions surrounding the exact mechanism of how HTS lowers ICP, the optimal concentration of HTS that is most effective in reducing ICP, the comparability of bolus infusion with continuous infusion, and whether HTS should be used as the first-line treatment. These questions must be answered conclusively to provide definitive guidelines for HTS therapy.

Three randomized controlled trials (RCTs) are needed. The first RCT will compare the effectiveness of different concentrations of HTS and mannitol, aiming to highlight the potential drawbacks of each treatment. The second RCT aims to compare the safety and efficacy of bolus and continuous infusion administration methods of osmotic agents. This investigation will provide valuable insights into the optimal way of administering osmotic agents while considering patient safety and treatment effectiveness concerns. The third RCT will compare HTS with current medical therapies to evaluate its advantages and disadvantages in treating elevated ICP. This assessment is crucial in determining where HTS stands among existing medical interventions for elevated ICP.

This review aims to create a strong foundation for future investigations. The main objective of these trials is to provide healthcare professionals with reliable and evidence-based information, allowing them to make better and safer decisions for their patients.

REFERENCES

1. Donkor ES. Stroke in the 21(st) Century: A Snapshot of the Burden, Epidemiology, and Quality of Life. Stroke Res Treat. 2018;2018:3238165.
2. Bamford J, Sandercock P, Dennis M, Burn J, Warlow C. Classification and natural history of clinically identifiable subtypes of cerebral infarction. Lancet. 1991;337(8756):1521-6.
3. Liebeskind DS, Jüttler E, Shapovalov Y, Yegin A, Landen J, Jauch EC. Cerebral Edema Associated With Large Hemispheric Infarction. Stroke. 2019;50(9):2619-25.
4. Gu Y, Zhou C, Piao Z, Yuan H, Jiang H, Wei H, et al. Cerebral edema after ischemic stroke: Pathophysiology and underlying mechanisms. Front Neurosci. 2022;16:988283.
5. Bardutzky J, Schwab S. Antiedema therapy in ischemic stroke. Stroke. 2007;38(11):3084-94.
6. Bereczki D, Liu M, Prado GF, Fekete I. Cochrane report: A systematic review of mannitol therapy for acute ischemic stroke and cerebral parenchymal hemorrhage. Stroke. 2000;31(11):2719-22.
7. Harutjunyan L, Holz C, Rieger A, Menzel M, Grond S, Soukup J. Efficiency of 7.2% hypertonic saline hydroxyethyl starch 200/0.5 versus mannitol 15% in the treatment of increased intracranial pressure in neurosurgical patients - a randomized clinical trial [ISRCTN62699180]. Crit Care. 2005;9(5):R530-40.
8. Daneman R, Prat A. The blood-brain barrier. Cold Spring Harb Perspect Biol. 2015;7(1):a020412.
9. Kadry H, Noorani B, Cucullo L. A blood-brain barrier overview on structure, function, impairment, and biomarkers of integrity. Fluids Barriers CNS. 2020;17(1):69.
10. Ballabh P, Braun A, Nedergaard M. The blood-brain barrier: an overview: structure, regulation, and clinical implications. Neurobiol Dis. 2004;16(1):1-13.
11. Gawdi R, Shumway KR, Emmady PD. Physiology, Blood Brain Barrier. StatPearls. Treasure Island (FL): StatPearls Publishing Copyright © 2024, StatPearls Publishing LLC.; 2024.
12. Shah MM, Mandiga P. Physiology, Plasma Osmolality and Oncotic Pressure. StatPearls. Treasure Island (FL): StatPearls Publishing Copyright © 2024, StatPearls Publishing LLC.; 2024.
13. Georgiadis AL, Suarez JI. Hypertonic saline for cerebral edema. Curr Neurol Neurosci Rep. 2003;3(6):524-30.
14. Fink ME. Osmotherapy for intracranial hypertension: mannitol versus hypertonic saline. Continuum (Minneap Minn). 2012;18(3):640-54
15. Mokri B. The Monro-Kellie hypothesis: applications in CSF volume depletion. Neurology. 2001;56(12):1746-8.
16. Hauer EM, Stark D, Staykov D, Steigleder T, Schwab S, Bardutzky J. Early continuous hypertonic saline infusion in patients with severe cerebrovascular disease. Crit Care Med. 2011;39(7):1766-72.
17. Al-Rawi PG, Tseng MY, Richards HK, Nortje J, Timofeev I, Matta BF, et al. Hypertonic saline in patients with poor-grade subarachnoid hemorrhage improves cerebral blood flow, brain tissue oxygen, and pH. Stroke. 2010;41(1):122-8.
18. Huang LQ, Zhu GF, Deng YY, Jiang WQ, Fang M, Chen CB, et al. Hypertonic saline alleviates cerebral edema by inhibiting microglia-derived TNF-α and IL-1β-induced Na-K-Cl Cotransporter up-regulation. J Neuroinflammation. 2014;11:102.
19. Mason A, Malik A, Ginglen JG. Hypertonic Fluids. StatPearls. Treasure Island (FL): StatPearls Publishing Copyright © 2024, StatPearls Publishing LLC.; 2024.
20. Koenig MA, Bryan M, Lewin JL, 3rd, Mirski MA, Geocadin RG, Stevens RD. Reversal of transtentorial herniation with hypertonic saline. Neurology. 2008;70(13):1023-9.
21. Froelich M, Ni Q, Wess C, Ougorets I, Härtl R. Continuous hypertonic saline therapy and the occurrence of complications in neurocritically ill patients. Crit Care Med. 2009;37(4):1433-41.
22. Lewandowski-Belfer JJ, Patel AV, Darracott RM, Jackson DA, Nordeen JD, Freeman WD. Safety and efficacy of repeated doses of 14.6 or 23.4 % hypertonic saline for refractory intracranial hypertension. Neurocrit Care. 2014;20(3):436-42.
23. Carter C, Human T. Efficacy, Safety, and Timing of 5% Sodium Chloride Compared With 23.4% Sodium Chloride for Osmotic Therapy. Ann Pharmacother. 2017;51(8):625-9.
24. Chugh AJS, Sunshine K, Srivatsa S, Maynard M, Shammassian BH, Hoffer SA. Effectiveness of Continuous Hypertonic Saline in Acute Ischemic Infarcts: A Radiographic and Clinical Evaluation. World Neurosurg. 2021;155:e503-e9.
25. Hirsch KG, Spock T, Koenig MA, Geocadin RG. Treatment of elevated intracranial pressure with

hyperosmolar therapy in patients with renal failure. Neurocrit Care. 2012;17(3):388-94.
26. Corry JJ, Varelas P, Abdelhak T, Morris S, Hawley M, Hawkins A, et al. Variable change in renal function by hypertonic saline. World J Crit Care Med. 2014;3(2):61-7.
27. Erdman MJ, Riha H, Bode L, Chang JJ, Jones GM. Predictors of Acute Kidney Injury in Neurocriti cal Care Patients Receiving Continuous Hyperton ic Saline. Neurohospitalist. 2017;7(1):9-14.
28. Schwarz S, Georgiadis D, Aschoff A, Schwab S. Effects of hypertonic (10%) saline in patients with raised intracranial pressure after stroke. Stroke. 2002;33(1):136-40.
29. Francony G, Fauvage B, Falcon D, Canet C, Dilou H, Lavagne P, et al. Equimolar doses of mannitol nd hypertonic saline in the treatment of increased intracranial pressure. Crit Care Med. 2008;36(3):795-800.
30. Diringer MN, Scalfani MT, Zazulia AR, Videen TO, Dhar R. Cerebral hemodynamic and metabolic effects of equi-osmolar doses mannitol and 23.4% saline in patients with edema following large ischemic stroke. Neurocrit Care. 2011;14(1):11-7.
31. S Su Y, Liu Y, Chen Z, Cui L. Comparison of equiosmolar doses of 10% hypertonic saline and 20% mannitol for controlling intracranial hyperten tion in patients with large hemispheric infarction. Clin Neurol Neurosurg. 2021;200:106359.
32. Larive LL, Rhoney DH, Parker D, Jr., Coplin WM, Carhuapoma JR. Introducing hypertonic saline for cerebral edema: an academic center experience. Neurocrit Care. 2004;1(4):435-40.
33. Sterns RH, Riggs JE, Schochet SS, Jr. Osmotic demyelination syndrome following correction of hyponatremia. N Engl J Med. 1986;314(24):1535-42.
34. Herpich F, Rincon F. Management of Acute Ischemic Stroke. Crit Care Med. 2020;48(11):1654-63.

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