Hypertonic Saline Solution Compared to Mannitol for the Management of Elevated Intracranial Pressure in Children: A Systematic Review

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Received: July 2023. Accepted: August 2023; Published: September 1, 2023.
Citation: Abdullah Saleh A. Alfarhan et al. Hypertonic Saline Solution Compared to Mannitol for the Management of Elevated Intracranial Pressure in Children: A Systematic Review. World Family Medicine. August 2023; 21(8): 105-111
DOI: 10.5742/MEWFM.2023.95256187

Abstract

Objective: To explore the effectiveness of commonly used dosing for mannitol (MN) compared with hypertonic saline solution (HSS) in children with elevated intracranial pressure (ICP) due to diabetic ketoacidosis (DKA), head trauma, or acute central nervous system (CNS) infections.

Methods: We followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. A structured literature review was carried out using the component of the PICO framework. The literature search was conducted in Medline, Ovid, Embase, Google Scholar, and PubMed. A combination of relevant search terms was used. Electronic searches were supplemented by manual searches of references of included studies and review articles. The duplicate citations were identified and removed.

Results: A total of 169 articles were identified through the searches, while 8 articles met the inclusion criteria. The characteristics and results of included studies were discussed, regarding the study design, sample size, and outcome.

Conclusions: Osmotic agents, such as HSS and MN are commonly used in the management of high ICP. HSS (3% or 7.5%) has superior therapeutic effects over MN (20%) in lowering increased ICP in children with cerebral edema.

Key Words: Cerebral edema, Increased intracranial pressure, Children, Osmotic agents, Mannitol, hypertonic saline solution, systematic review, PRISMA.

Introduction

Increased intracranial pressure (ICP) is a common health problem, which is frequently triggered by brain edema. As high ICP is related to increased death and impaired functional results, its control is quite important (1-2). Osmotic agents are commonly used to reduce elevated ICP, improve cerebral perfusion pressure, and presumably improve cerebral blood flow. Yet, osmotic agents have other physiological effects that can influence cerebral blood flow (3).

Elevated ICP pressure has a major impact on the worsening of the patient's neurologic status, through the impairment of brain perfusion. To reduce the intensity and the time spent with increased ICP, the infusion of MN has been recommended as a first-line agent. However, the side effects of MN are significant. In traumatic brain injury, 3% hypertonic saline solution (HSS) shows varied results in comparison with 20% MN (4). The growing interest in the use of 3% HSS has challenged the use of MN (5).

Hypertonic saline solution (HSS) and MN are osmotic agents that are commonly used in the management of high ICP. However, the clinical advantage of one over the other has not been confirmed (6). The effectiveness of MN in the management of elevated ICP, and its complications are still unclear (7). There are limited randomized controlled trials (RCTs) that have compared mannitol and 3% HSS regarding their ability to reduce ICP (8-10). However, since the magnitude of brain shrinkage depends mostly on the depth of the osmotic gradient established between plasma and brain tissue compartments, such comparisons about the respective effectiveness of MN and 3% HSS in reducing ICP are difficult to interpret (4).

Although osmotic agents have been utilized to reduce cerebral edema for nearly 5 decades, significant controversy regarding the choice of agent and dosing exists (11). Since mannitol and HSS may differ regarding their clinically relevant mechanisms of action, there is a need to determine which osmotic compound could be the most appropriate for patients with elevated ICP (4).

The available studies comparing mannitol with HSS in the management of children with raised ICP are quite scarce (12). Therefore, we undertook this systematic review to explore the effectiveness of commonly used dosing for mannitol compared with HSS in children with raised ICP due to diabetic ketoacidosis, head trauma, or acute CNS infections.

Materials and Methods

Research question

In children with increased ICP (or cerebral edema), is it better to administer MN or 3% HSS?

The PICO framework was followed to develop the review questions, as follows:

- P (Population): Children with increased ICP (or cerebral edema)
- I (Intervention): 3% Hypertonic saline solution.
- C (Comparator): Mannitol.
- O (Outcome): Lowering ICP.

Literature search

We followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. A structured literature review was carried out using the component of the PICO framework. The literature search was conducted in Medline, Ovid, Embase, Google Scholar, and PubMed.

Combinations of the following search terms were used: intracranial pressure, type 1 diabetes, diabetic ketoacidosis, head trauma, cerebral edema, cerebral hypertension, mannitol, hypertonic saline. No search for grey literature or unpublished literature was performed.

Electronic searches were supplemented by manual searches of references of included studies and review articles. The duplicate citations were identified and removed.

Two reviewers (ASAA and SAMA) independently assessed the quality of studies using the Newcastle–Ottawa Scale quality assessment tool for observational studies. To reach a consensus, all different opinions about quality assessment were discussed with a third senior reviewer (KMSA).

Inclusion and exclusion criteria

We included studies that met the following criteria:

- Free full-text articles published in the English language in the last 10 years (2003-2022).
- Articles reporting on comparative management of increased ICP among children by both MN and 3% HSS.

The exclusion criteria were:

- Single case reports or case series, abstracts, review articles, and commentaries to articles.
- Articles reporting exclusively on adult cases.
- Articles reporting on the management of increased ICP either by MN only or by HSS only.

Data extraction

The following data were extracted from retrieved articles: publication year, study characteristics, sample size, research design, assessment points, measures used, number of assessments during pregnancy, onset, course, and prevalence rates.

Results and Discussion

Study characteristics

Figure (1) presents the PRISMA flow chart, showing that of 169 articles identified through the searches;, eight articles met the inclusion criteria of comparing the outcome of treatment of increased ICP/cerebral edema among children by MN or HSS. The characteristics and results of the included studies are summarized in Table (1).

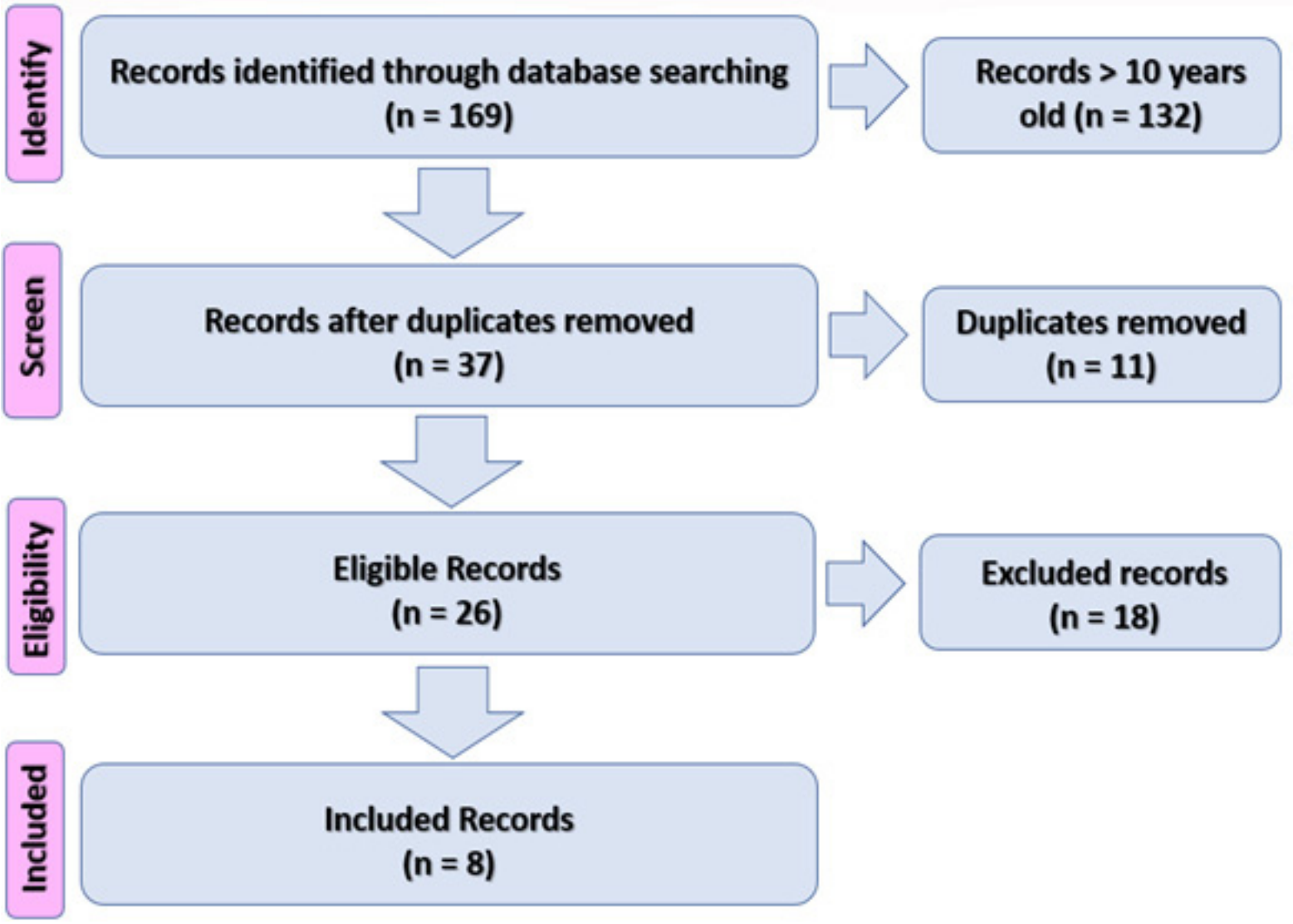

Table 1: Summary of the main results

Authors	Year	Study design	Sample size	Diagnosis	Dose	Outcome
Vialet et al. [8]	2003	RCT	7.5% HSS: 10 20% MN: 10	Raised ICP due to head trauma	HSS: 2 mL/kg bw of 2400 mOsm/kg/H_2O MN: 2 mL/kg bw of 1160 mOsm/kg/H_2O	HSS > MN
Battison et al. [13]	2005	Cross-over RCT	9 patients	ICP >20 mmHg due to head trauma or subarachnoid hemorrhage	100 mL of 7.5% HSS + 6% dextran-70 solution over 5 mins MN: Rapid IV infusions of 200 mL	HSS > MN
Yildizdas et al. [15]	2006	Retrospective	3% HSS: 25 MN: 22 Both: 20	Cerebral edema due to intracranial hemorrhage, encephalopathy, meningitis	HSS: 0.5-2 mL/kg/h infusion rate. Each bolus was applied as 1 mL/kg for 15 min. MN: 0.5 g/kg for the first 2 doses. Maintenance: 0.25 g/kg/dose	HSS > MN
Kumaraguru et al. [14]	2012	RCT	3% HSS: 40 20% MN: 40	Cerebral edema due to DKA	HSS: 5ml/kg IV, over 20 min/8 hrs MN: 1.5ml/kg IV, over 20 min/8 hrs	HSS = MN
DeCourcey et al. [16]	2013	Retrospective	3% HSS: 299 20% MN: 1202 Both: 131	Cerebral edema due to DKA	---	HSS > MN
Rameshkumar et al.[12]	2020	RCT	3% HSS: 29; 20% MN: 28	Raised ICP due to CNS infection	HSS: 10 mL/kg loading, followed by 0.5–1 mL/kg/hr infusion MN: 0.5 gram/kg/dose	HSS > MN
Wellard et al. [17]	2021	Retrospective	3% HSS: 17 20% MN: 5 HSS + MN: 8	Raised ICP due to head trauma	---	HSS > MN
Kochanek et al. [18]	2022	Retrospective	HSS: 192; MN: 159	Traumatic brain injury	---	HSS > MN

ICP: Intracranial pressure HSS: Hypertonic saline solution MN: Mannitol
RCT: Randomized controlled trial DKA: Diabetic ketoacidosis CNS: Central nervous system

This systematic review included four RCTs (8; 13-14); and Rameshkumar et al. (12), in addition to four retrospective studies (15-18).

The included eight studies had variable sample sizes, ranging from nine children in the cross-over RCT (13) and 10 children receiving HSS compared with 10 children receiving MN in the RCT of Vialet et al. (8) to 1632 (299 received HSS; 1202 received MN: 1202; and 131 received both HSS and MN).

The studies included in the present systematic review comprised children with cerebral edema as a result of different causes, mainly diabetic ketoacidosis (14; 16), central nervous system infections (12; 15), or head trauma (8; 13; 17-18).

Nehring et al. (19) described different causes of cerebral edema. For example, "cellular or cytotoxic" edema often results within minutes of the insult and affects glial, neuronal, and endothelial cells within the brain. In cytotoxic edema, the cells lack hemostatic mechanisms, and primarily sodium enters the cell freely, with the failure of the export mechanism. Traumatic brain injury causes this form of edema.

Nehring et al. (19) added that "interstitial" cerebral edema results from the outflow of cerebrospinal fluid from the intraventricular space to the interstitial areas of the brain. Patients with meningitis are examples of those affected by this etiology. Moreover, "osmotic" edema generally stems from derangements affecting osmolarity, such as hyponatremia, diabetic ketoacidosis (DKA), or similar metabolic pathologies.

Murad et al. (20) noted that various versions describing the hierarchy (i.e., pyramid) of evidence focused on showing weaker study designs at the bottom (e.g., basic science and case series), followed by case–control, and cohort (prospective and retrospective) studies in the middle, then at the very top the RCTs, and systematic reviews. The quality of obtained evidence drives the strength of recommendations, which is one of the last translational steps of research.

The present systematic review compared the outcome of children with cerebral edema after being treated with MN and/or HSS. The commonly prescribed concentration of MN was 20%, while that for HSS was mainly 3%, but the HSS concentrations used in the studies of Vialet et al. (8) and Battison et al. (13) were 7.5%.

It is to be noted that children with cerebral edema should be promptly controlled to prevent further injury, and complications, such as increased ICP. Avoidance of hypotonic fluids is a strong recommendation in instances of cerebral edema as they can worsen the condition and cause elevations in ICP. Various methods are available to help control ICP, such as positioning, and hyperosmolar therapy (19).

Desai and Damani (21) stressed that hyperosmolar therapy is the cornerstone for the management of patients with increased ICP. It is used in various pathologies and has become a valuable therapy in modern neurological critical care worldwide, which has stood the test of time. The discovery of hyperosmolar therapy has not only provided a wealth of data for the management of increased ICP, but has also allowed us to develop new treatment strategies by improving our understanding of the molecular mechanisms of cerebral inflammation, blood-brain permeability, and cerebral edema in all modes of neuronal injury.

Hypertonic saline solution (HSS) and MN are examples of osmotic agents used in the management of high ICP. Their ICP-decreasing properties are well known (6). Rameshkumar et al. (12) noted that the side effects of mannitol, like osmotic diuresis and hypotension, are significant and can lead to increased morbidity. Due to this, HSS has been compared with 20%-mannitol in patients with cerebral edema but with variable results.

Findings of the present systematic review indicate the superiority of HSS (3% or 7.5%) over 20% mannitol for the management of increased ICP.

This finding is in accordance with those reported by several RCTs, showing higher effectiveness on ICP after an infusion of 3% HSS than after an equimolar infusion of MN (4). Moreover, a longer duration of ICP reduction was observed after the use of 3% HSS, due to the combination of HSS with 6% hydroxyethyl starch solution or with 6% dextran solution (13), which are known to prolong the effects of HSS.

Adelson et al. (22) argued that although MN continues to be the most commonly used hyperosmotic agent for the management of cerebral edema, there is increasing evidence of the superior benefits of HSS. Although much of the research on HSS use in pediatrics is retrospective, there is sufficient evidence present for HS to be included as a better option for hyperosmolar therapy.

Brenkert et al. (23) found that about one-third of their DKA patients with a concern for cerebral edema received HSS. However, a consensus statement on the treatment of DKA in children and adolescents recommends prompt treatment of suspected cerebral edema with MN. Nevertheless, the diuresis potentially seen with MN may lead to unwanted adverse effects, such as intravascular dehydration, hypotension, prerenal azotemia, and even decreased cerebral blood flow (24).

Based on case reports and expert consensus, Dunger et al. (25) reported that there are no definite beneficial effects with the use of MN over HSS, which is a better alternative to MN use. Similarly, Curtis et al. (26) described a 13-year-old in DKA with a declining Glasgow Coma Scale score despite receiving a total of 0.7 g/kg of MN. A 5-mL/kg dose of 3% HSS was rapidly infused with the return of the patient's Glasgow Coma Scale score to 15 within five minutes. There were no signs of neurological damage at the time of discharge.

Kamat et al. (24) also described the use of 3% HSS in 4 patients with altered mental status and DKA. Each patient received at least one bolus at a dose of 10 mL/kg over 30 minutes. All patients showed improvement in neurological status, and no adverse effects of therapy were described.

Yildizdas et al. (15) stated that HSS has also been shown to be effective in the management of cerebral edema of infectious, anoxic, hemorrhagic, and metabolic origin. In children with cerebral edema secondary to non-traumatic causes, 3% HSS use was associated with significantly lower mortality rates and shorter duration of a comatose state when compared with MN.

Study Limitations

This study included free full-text articles published in the English language and the focus was on the last 10 years. There were only 9 eligible studies fulfilling the inclusion criteria. Despite the inclusion of four RCTs, which occupy the top of the hierarchy of evidence, five retrospective studies were included, which lie in the middle of the hierarchy of evidence and are usually associated with the risk of recall bias (24).

Conclusion

Osmotic agents, such as HSS and MN are commonly used in the management of high ICP. HSS (3% or 7.5%) has superior therapeutic effects over MN (20%) in lowering increased ICP in children with cerebral edema.

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