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Review

Optimal Dose and Concentration of Hypertonic Saline in Traumatic Brain Injury: A Systematic Review

Travmatik Beyin Hasarında Hipertonik Salinin Optimal Dozu ve Konsantrasyonu: Sistematik Bir İnceleme

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ABSTRACT

Management of increased intracranial pressure in traumatic brain injury remains challenging in neurosurgical emergencies. The mainstay of medical management for increased intracranial pressure is hyperosmolar therapy with mannitol or hypertonic saline. Mannitol has been the "gold standard" osmotic agent for almost a century. Given its wide usage, there has been a dilemma of concern because of its adverse effects. Over the past few decades, hypertonic saline has become an increasingly better alternative. To date, there is no consensus on the optimal therapeutic dose and concentration of hypertonic saline for treating increased intracranial pressure. This systematic review aimed to compare the efficacy of hypertonic saline and mannitol in the management of traumatic brain injury and investigate the optimal dose and concentration of hypertonic saline for the treatment. Extensive research was conducted on PubMed, DOAJ, and Cochrane databases. Studies published within the last 20 years were included. Research articles in the form of meta-analyses, clinical trials, and randomized controlled trials were preferred. Those with ambiguous remarks, irrelevant correlations to the main issue, or a focus on other disorders were excluded. Nineteen studies were included in the systematic review. Eleven studies have stated that hypertonic saline and mannitol were equally efficacious, whereas eight studies have reported that hypertonic saline was superior. Moreover, 3% hypertonic saline was the main concentration most discussed in research. Improvements in increased intracranial pressure, cerebral perfusion pressure, survival rate, brain relaxation, and systemic hemodynamics were observed. Hypertonic saline is worthy of consideration as an excellent alternative to mannitol. This study suggests 3% hypertonic saline as the optimal concentration, with the therapeutic dose from 1.4 to 2.5 mL/kg, given as a bolus.

Keywords: Hypertonic saline, intracranial pressure, mannitol, traumatic brain injury

ÖZ

Travmatik beyin hasarında artan kafa içi basıncının yönetimi, beyin cerrahisi acillerinde zorlayıcı olmaya devam etmektedir. Artmış kafa içi basıncı için tıbbi tedavinin temeli, mannitol veya hipertonik salin ile hiperozmolar tedavidir. Mannitol, neredeyse bir asırdır "altın standart" ozmotik ajan olmuştur. Geniş kullanımı göz önüne alındığında, olumsuz etkileri nedeniyle endişeli bir ikilem oluşturmuştur. Son birkaç on yılda, hipertonik salin giderek daha iyi bir alternatif haline geldi. Bugüne kadar, artan kafa içi basıncını tedavi etmek için optimal terapötik doz ve hipertonik salin konsantrasyonu üzerinde bir fikir birliği yoktur. Bu sistematik derleme, travmatik beyin hasarının tedavisinde hipertonik salin ve mannitolün etkinliğini karşılaştırmayı ve tedavi için optimal hipertonik salin dozunu ve konsantrasyonunu araştırmayı amaçladı. PubMed, DOAJ ve Cochrane veri tabanları üzerinde kapsamlı araştırmalar yapıldı. Son 20 yılda yayınlanan çalışmalar dahil edildi. Meta-analizler, klinik çalışmalar ve randomize kontrollü çalışmalar tercih edildi. Belirsiz açıklamalar, ana konuyla alakasız korelasyonlar veya diğer bozukluklara odaklananlar hariç tutuldu. Sistematik derlemeye 19 çalışma dahil edildi. On bir çalışma hipertonik salin ve mannitolün eşit derecede etkili olduğunu belirtirken, sekiz çalışma hipertonik salinin üstün olduğunu bildirmiştir. Ayrıca, araştırmada en çok tartışılan ana konsantrasyon %3 hipertonik salindi. Artmış kafa içi basıncı, serebral perfüzyon basıncı, hayatta kalma oranı, beyin relaksasyonu ve sistemik hemodinamikteki iyileşmeler gözlendi. Hipertonik salin, mannitole mükemmel bir alternatif olarak dikkate alınmaya değerdir. Bu çalışma, bolus olarak verilen 1,4 ila 2,5 mL/kg terapötik dozla optimal konsantrasyon olarak %3 hipertonik salin önermektedir.

Anahtar kelimeler: Hipertonik salin, kafa içi basınç, mannitol, travmatik beyin hasarı

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INTRODUCTION

Traumatic brain injury (TBI) is one of the most common causes of death and disability worldwide[1,2]. Secondary increased intracranial pressure (ICP) is highly prevalent after a severe TBI, and it is usually caused by brain edema[1]. Increased ICP as a result of TBI has been linked to an increased risk of morbidity, death, and functional impairment[1,2].

Mortality of 18.4% was recorded among patients with ICP<20 mmHg, whereas 55.6% mortality was registered in patients with ICP>40 mmHg[2,3]. The Brain Trauma Foundation recommends that ICP management should be promptly performed when ICP rises >20 mmHg and recommends ICP monitoring to guide therapy[2-4]. Current guidelines recommend more conservative measures such as elevation of the upper body, cerebrospinal fluid (CSF) drainage, sedation and paralysis, hyperventilation, barbiturates, hypothermia, and hyperosmolar therapy before decompressive craniectomy[1,2]. The mainstay of medical management for increased ICP is hyperosmolar therapy with mannitol or hypertonic saline (HTS)[4,5]. Hyperosmolar therapy lowers ICP and improves cerebral perfusion pressure (CPP) and cerebral blood flow (CBF)[1].

Mannitol is still the main choice for hyperosmolar therapy to treat increased ICP in TBI. However, given its wide usage, there has been dissatisfaction and concern about its serious side effects. HTS is now receiving widespread attention as an alternative to mannitol, and several recent studies have demonstrated its increasing effectiveness[3]. However, there is currently no consensus on the optimal therapeutic dose and concentration of HTS for treating increased ICP[6]. Thus, this systematic review aimed to compare the efficacy of HTS and mannitol in TBI management and investigate the optimal dose and concentration of HTS for the treatment.

MATERIALS and METHODS

Search Strategies

This systematic review used Preferred Reporting Items for Systematic Review and Meta-analysis (PRISMA) protocols. The Patient, Intervention, Comparsion, and Outcome (PICO) framework was also used to develop the eligibility criteria. Table 1 shows the PICO criteria. Extensive search was conducted on PubMed, DOAJ, and Cochrane databases. To conduct more inquiries, the following keywords were employed: "mannitol" or "hypertonic" or "saline" or "intracranial" or "pressure" or "traumatic" or "brain" or "injury." Articles published within the last 20 years were included.

Filtering Process

According to the PRISMA statement, titles and abstracts of the records retrieved were screened, and full texts of those considered relevant were analyzed. Full-text articles in the form of meta-analyses, clinical trials, and randomized controlled trials were preferred; thus, a total of 24 studies were selected. Finally, 19 studies were included in this systematic review. Moreover, five articles were eliminated because of similarity to other articles, ambiguous remarks, irrelevant correlations to the main issue, or a focus on disorders other than TBI. Figure 1 shows the PRISMA flow diagram for the identification and selection process of relevant articles, whereas Table 2 shows the list of articles that made up the systematic review.

RESULTS

We identified a total of 130 studies using the initial search method. Because of the non-relevant titles, 87 studies were excluded, leaving 43 studies with relevant titles. Nineteen studies were eliminated based on title and abstract screening. Experimental animal studies and literature review articles were excluded. Finally, 19 studies were included in this systematic review after screening and qualitative evaluation.

Eight studies have suggested that HTS is more effective than mannitol for the management of increased ICP in TBI[6-13]. Patil and Gupta[7] experimented with three osmotic agents, which demonstrated comparable effectiveness in lowering ICP when the same osmotic load was administered; however, 3% HTS was found to be the most effective, followed by a combination of 10% mannitol + 10% glycerol and 20% mannitol. The 3% HTS with an initial bolus dose of 1.4 mL/kg may be recommended to treat patients with hypovolemia, hyponatremia, or renal failure[7]. Shi et al.[6] also mentioned that 3% HTS had a longer-lasting effect on ICP and may be effective in improving CPP. Bhatnagar et al.[8] examined the effects of

Table 1. PICO formulation.

Patient/problem (P)	Intervention (I)	Comparison (C)	Outcome (C)
Increased intracranial pressure in patients with traumatic brain injury	Hypertonic saline	Mannitol	Intracranial pressure improvement
Type of clinical question	Intervention		
Study design	Meta-analyses, clinical trials, and randomized controlled trials		

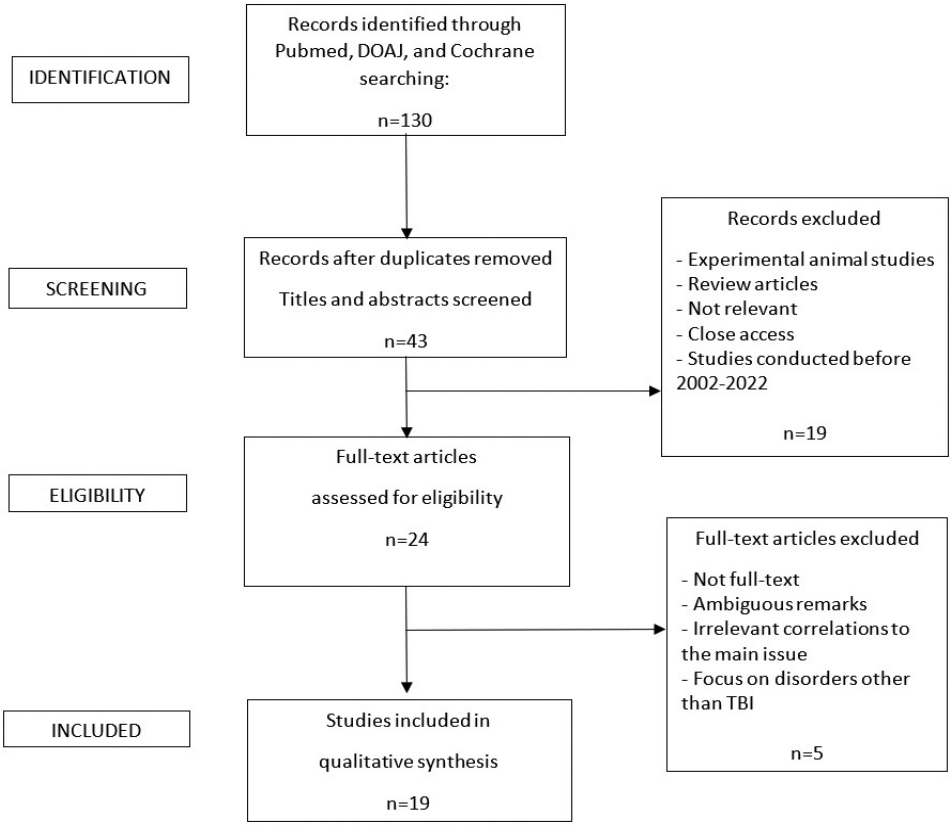

Figure 1. PRISMA flow diagram for the identification and selection process.
TBI: Traumatic brain injury

300 mL 20% mannitol only or 300 mL 20% mannitol + 150 mL 3% HTS or 300 mL 3% HTS on intraoperative events during decompressive craniectomy in TBI and concluded that 300 mL 3% HTS was more effective in improving Glasgow coma scale (GCS) in patients with severe TBI. Cheng et al.[9] stated that when used in equimolar doses, the reduction in the ICP of patients with TBI achieved with 3% HTS bolus was superior to that achieved with 20% mannitol after decompressive craniectomy, although this advantage did not appear to confer any additional benefit terms of short-term mortality. For the management of refractory posttraumatic intracranial hypertension, Vialet et al.[10] reported that HTS is effective and safe as an initial treatment of increased ICP in individuals with head trauma. Infusion of 2 mL/kg of 7.5% HTS was more efficacious than administering 2 mL/kg of 20% mannitol for the management of bouts of refractory increased ICP in patients with severe TBI[10].

Another 11 studies have concluded that mannitol and HTS had similar effectiveness in reducing ICP with given in equimolar concentrations, producing comparable effects on intracranial reduction, CPP improvement, survival rate, brain relaxation, and systemic hemodynamics[1-3,14-21]. Tatro et al.[14] found no significant difference in the primary endpoint absolute reduction of ICP at 30, 60, or 120 min after infusion of hyperosmolar treatment with 30 mL of 23.4% HTS or 0.5 g/kg mannitol in a trial. Han et al.[1] also noted that HTS had no significant effect on the favorable outcome, mortality, ICP 90-120 min after infusion termination, CPP 90-120 min after infusion termination, and duration of increased ICP per day compared with mannitol. Although their study did not lend a specific recommendation to select HTS or mannitol as first-line treatment, Gu et al.[20] mentioned that HTS appeared preferable in cases of refractory intracranial hypertension. Additionally, Francony et al.[15] reported that infusion of 100 mL of 7.45% HTS was as efficacious as 231 mL of 20% mannitol in decreasing ICP, but mannitol exerted additional effects on cerebral circulation by possibly increasing rheology. According to Chen et al.[2], only weak evidence suggested that HTS was no better than mannitol in terms of efficacy and safety in the long-term management of acute TBI.

Table 2. Studies that made up the systematic review.

S	Year	Title	Study design	Samples	Results	Conclusion	Reference
Kochanek et al.	2022	Comparison of intracranial pressure measurements before and after hypertonic saline or mannitol treatment in children with severe traumatic brain injury	Observational comparative study	518	✓	During ICP crises, hypertonic saline (HTS) was associated with better performance than mannitol.	11
Bhatnagar et al.	2021	Effects of two different doses of 3% hypertonic saline with mannitol during decompressive craniectomy following traumatic brain injury: A prospective, controlled study	Prospective controlled study	90	✓	Increasing osmotic load by addition of 3% HTS to mannitol provides better intraoperative brain relaxation than mannitol alone during decompressive craniectomy. An addition of 300 mL of 3% HTS was more effective in improving GCS in patients with severe TBI.	8
Schwimmbeck et al.	2021	Hypertonic saline versus mannitol for traumatic brain injury: A systematic review and meta-analysis with trial sequential analysis	Systematic review and meta-analysis	464 (of 12 trials)	✓	HTS might be superior to mannitol in the treatment of TBI-related increased ICP.	13
Shi et al.	2020	Hypertonic saline and mannitol in patients with traumatic brain injury: A systematic and meta-analysis	Meta-analysis	544 (of 10 trials)	✓	3% HTS has a more sustained effect on the ICP and can effectively increase cerebral perfusion pressure.	6
Patil and Gupta	2019	A comparative study of bolus dose of hypertonic saline, mannitol, and mannitol plus glycerol combination in patients with severe traumatic brain injury	Randomized controlled trial	120	✓	3% HTS appeared to be more effective followed by 10% mannitol + 10% glycerol combination and 20% mannitol.	7
Cheng et al.	2018	A retrospective study of intracranial pressure in head-injured patients undergoing decompressive craniectomy: A comparison of hypertonic saline and mannitol	Retrospective study	60	✓	When used in equiosmolar doses, the reduction in the ICP of patients with TBI achieved with 3% HTS was superior to that achieved with mannitol after decompressive craniectomy. However, this advantage did not appear to confer any additional benefit in terms of short-term mortality.	9

Table 2. continued

S	Year	Title	Study design	Samples	Results	Conclusion	Reference
Kamel et al.	2011	Hypertonic saline versus mannitol for the treatment of elevated intracranial pressure: a meta-analysis of randomized clinical trials	Meta-analysis	112 (of 5 trials)	✓	HTS is more effective than mannitol for the treatment of elevated ICP.	12
Vialet et al.	2003	Isovolume hypertonic solutes (sodium chloride or mannitol) in the treatment of refractory posttraumatic intracranial hypertension: 2 mL/kg 7.5% saline is more effective than 2 mL/kg 20% mannitol	Randomized controlled trial	20	✓	When a hypertonic solute was required for the treatment of refractory intracranial hypertension episodes in patients with severe head trauma, increasing the osmotic load by giving 2 mL/kg (body weight) of 7.5% saline (361 +/- 13 mOsm) was more effective than giving 2 mL/kg (body weight) of 20% mannitol (175 +/- 12 mOsm).	10
Han et al.	2022	Hypertonic saline compared to mannitol for the management of elevated intracranial pressure in traumatic brain injury: A meta-analysis	Meta-analysis	1392 (of 17 trials)	=	HTS had no significant effect on the favorable outcome, mortality, ICP 90-120 min after infusion termination, cerebral perfusion pressure 90-120 min after infusion termination, and duration of elevated ICP per day compared with mannitol in participants with TBI. However, HTS had a significantly lower treatment failure rate, lower ICP 30-60 min after infusion termination, and higher cerebral perfusion pressure 30-60 min after infusion termination compared with mannitol in participants with TBI.	1
Tatro et al.	2021	23.4% Sodium chloride versus mannitol for the reduction of intracranial pressure in patients with traumatic brain injury: A single-center retrospective cohort study	Retrospective cohort study	31	=	No difference was found for the absolute reduction of ICP at 30, 60, and 120 min after the infusion of hyperosmolar agent or time to next elevated ICP.	14

Table 2. continued

S	Year	Title	Study design	Samples	Results	Conclusion	Reference
Miyoshi et al.	2020	Effects of hypertonic saline versus mannitol in patients with traumatic brain injury in prehospital, emergency department, and intensive care unit settings: a systematic review and meta-analysis	Systematic review and meta-analysis	125 (of 4 trials)	=	No significant difference was found in the all-cause mortality rates between patients receiving HTS or mannitol to control ICP.	19
Huang et al.	2020	Equimolar doses of hypertonic agents (saline or mannitol) in the treatment of intracranial hypertension after severe traumatic brain injury	Randomized controlled trial	83	=	Repeat bolus dosing of 10% HTS and 20% mannitol appears to be significantly and similarly effective for treating intracerebral hemorrhage in patients with severe TBI. The proportion of efficacious doses of HTS on ICP reduction may be higher than mannitol.	3
Chen et al.	2020	Hypertonic saline versus other intracranial pressure-lowering agents for people with acute traumatic brain injury	Meta-analysis	287 (of 6 trials)	=	Based on limited data, weak evidence suggests that HTS is no better than mannitol in efficacy and safety in the long-term management of acute TBI.	2
Kumar et al.	2019	Comparison of equiosmolar dose of hyperosmolar agents in reducing intracranial pressure-a randomized control study in pediatric traumatic brain injury	Randomized controlled trial	30	=	Mannitol and HTS were equally effective for the treatment of increased ICP in children with severe TBI.	18
Gu et al.	2019	Hypertonic saline or mannitol for treating elevated intracranial pressure in traumatic brain injury: a meta-analysis of randomized controlled trials	Meta-analysis	438 (of 12 trials)	=	The results do not lend a specific recommendation to select HTS or mannitol as a first-line treatment for patients with TBI-induced elevated ICP.	20
Jagannatha et al.	2016	An equiosmolar study on early intracranial physiology and long-term outcome in severe traumatic brain injury comparing mannitol and hypertonic saline	Randomized controlled trial	38	=	Immediate physiological advantages seen with HTS over mannitol did not translate into long-term benefit on ICP/CPP control or mortality of patients with TBI.	17

Table 2. continued

S	Year	Title	Study design	Samples	Results	Conclusion	Reference
Huang and Yang	2014	Comparison of 20% mannitol and 15% hypertonic saline in doses of similar osmotic burden for treatment of severe traumatic brain injury with intracranial hypertension	Randomized controlled trial	33	=	Treatment with 15% HTS and mannitol in doses of similar osmotic burden produces comparable effects in the management of increased ICP in patients with severe TBI in terms of the time of action onset, maximum ICP reduction, and duration of action.	16
Rickard et al.	2014	Salt or sugar for your injured brain? A meta-analysis of randomised controlled trials of mannitol versus hypertonic sodium solutions to manage raised intracranial pressure in traumatic brain injury	Meta-analysis	171 (of 6 trials)	=	Evidence shows that both agents effectively lower ICP.	21
Francony et al.	2008	Equimolar doses of mannitol and hypertonic saline in the treatment of increased intracranial pressure	Randomized controlled trial	20	=	A single equimolar infusion of 20% mannitol is as effective as 7.45% HTS in decreasing ICP in patients with brain injury.	15

ICP: Intracranial pressure, GCS: Glasgow coma scale, HTS: Hypertonic saline, TBI: Traumatic brain injury

In treating severe TBI with intracranial hypertension, four studies have concluded that HTS and mannitol were significantly equally efficacious in treating increased ICP in those with severe TBI[3,16-18]. Huang et al.[3] revealed that repeated bolus doses of 0.63 mL/kg 10% HTS and 2 mL/kg 20% mannitol appeared considerably and equally effective in managing intracerebral hemorrhage in individuals with severe TBI. In addition, Huang and Yang[16] revealed that 0.42 mL/kg 15% HTS bolus and 2 mL/kg 20% mannitol in the same osmotic load dose produced a comparable effect in the management of increased ICP in severe TBI in terms of onset of action, maximum ICP reduction, and duration of action. Jagannatha et al.[17] emphasized that the immediate physiologic benefit of 2.5 mL/kg 3% HTS bolus over 2.5 mL/kg 20% mannitol did not imply any long-term benefit in reducing ICP, CPP, or death in patients with TBI.

Kochanek et al.[11] conducted an observational study in children with severe TBI and revealed that bolus administration of 3% HTS was associated with lower ICP and improved CPP, whereas mannitol was simply linked to improved CPP. Kumar et al.[18] also found that both 2.5 mL/kg 3% HTS bolus and 20% mannitol were similarly beneficial for treating children with severe TBI.

DISCUSSION

The first study that hypertonic fluid had the potential to lower intracranial pressure while also shrinking nerve tissue was reported by Weed and McKibben in 1919[6,22]. Then, in 1935, Fay tested intravenous hypertonic sodium and magnesium solutions in the study "The Treatment of Acute and Chronic Cases of Cerebral Trauma, By Methods of Dehydration." It was not until the early 1960s that mannitol began to be used more widely and became the agent of choice after ICP monitoring was first used in the case of a brain injury[22]. HTS was first recognized as a possibly more effective alternative for hemorrhagic shock resuscitation, where the benefit of improved survival was indicated when used for patients with head injury complicated with hemorrhagic shock[2].

Mannitol has been recommended as the "gold standard" osmotic agent for almost a century, and its widespread use has raised concerns about hypotension, particularly in patients with hypovolemia, rebound phenomenon with increased ICP, and renal damage due to an increase in serum osmolarity[3,19]. Mannitol is commonly administered as a 0.25 g/kg to 1 g/kg body weight bolus, which can be repeated every 2-6 h. ICP is reduced within 1-5 min after receiving an intravenous bolus of mannitol, with a peak effect between 20 and 60 min[23]. Mannitol acts by its osmotic diuretic properties, which draw edema fluid from the cerebral parenchyma, leading to a reduction in cerebral water content and CSF pressure. This process takes 15-30 min or a gradient to form[23,24]. Additionally, it lowers ICP by altering blood fluid dynamics or blood rheology[24]. An increase in plasma volume, as well as a drop in hematocrit and blood viscosity, occurs immediately after mannitol infusion, which may improve CBF and, on balance, oxygen delivery to the brain. The infusion of mannitol promotes cerebral vasoconstriction, which results in a steady CBF and a lower ICP. Serum osmolarity should be maintained at less than 320 mOsm to avoid adverse effects, such as hypovolemia, hyperosmolarity, and renal failure[23].

Over the last few decades, HTS has become an increasingly better alternative, and several recent studies have demonstrated comparable effectiveness[3]. The concentration of HTS commonly used varies from 3.0% to 23.4%, and HTS is given at doses from 1.0 to 4.0 mL/kg as a bolus or continuous infusion[6,7,23,25]. Generally, boluses were administered at 4- to 6-h intervals, whereas continuous infusion of HTS infusate was given from the initiation to termination of therapy[25]. In the presence of an intact blood-brain barrier, HTS provides an osmotic force that draws water from the interstitial spaces of the brain parenchyma into the intravascular compartment, lowering the intracranial volume and ICP[23]. Because of its diuretic effect, mannitol is contraindicated in patients with hypovolemia, whereas HTS has no diuretic effect and hence maintains hemodynamic stability and CPP[23,24].

In this systematic review, 3% HTS was the main concentration most discussed in seven studies. The dose range given to the patient in these studies was 1.4 to 2.5 mL/kg. Additionally, Bhatnagar et al.[8] suggested that 300 mL of 3% HTS was efficacious in improving GCS in patients with severe TBI. Furthermore, five studies have suggested that 3% HTS might be superior to mannitol in the treatment of TBI, whereas two studies have suggested that 3% HTS and mannitol were equally effective. Bolus administration of 3% HTS was preferred over continuous infusion[6-9,11,17,18].

This systematic review also discussed other concentrations of HTS, including 7.45%, 7.5%, 10%, 15%, and 23.4%, and each of these was discussed in one study[3,10,14-16]. Seven other studies have not examined specific doses and concentrations of HTS[1,2,12,13,19-21]. Only 7.5% HTS was reported to be superior to mannitol, whereas others were reported to have the same efficacy as mannitol[3,10,14-16].

Secondary bleeding due to decreased platelet aggregation and delayed coagulation time, hypokalemia, and hyperchloremic acidosis are some of the adverse effects of HTS therapy[23]. Fortunately, this devastating condition has been rarely observed[4]. Hyponatremia has to be ruled out before administering HTS because the rapid increase in serum sodium content caused by HTS raises concerns about central pontine myelinolysis[4,23].

CONCLUSIONS

HTS is worthy of consideration as an excellent alternative to mannitol. This study suggests 3% HTS as the optimal concentration, with the therapeutic dose from 1.4 to 2.5 mL/kg, given as a bolus. Further research and consensus are essential to determine the best therapeutic dose and concentration of HTS.

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Ethics

Peer-review: Externally and internally peer-reviewed.

Author Contributions

Surgical and Medical Practices: M.S., I.R., Concept: M.S., I.R., Design: M.S., I.R., Data Collection and/or Processing: M.S., I.R., Analysis and/or Interpretation: M.S., I.R., Literature Search: M.S., I.R., Writing: M.S., I.R.

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