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REVIEW ARTICLE

Is hypertonic saline an effective alternative to mannitol in the treatment of TBI in adult and pediatric patients? A systematic review and meta-analysis

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ABSTRACT

Aim: This meta-analysis and systematic review aims to investigate and compare the efficacy of mannitol and hypertonic saline in treating patients who have suffered from traumatic brain injury (TBI).

Methods: We reviewed publications from the Medline database, Web of Science, and Google Scholar from inception to 13 October 2022 with only English-based literature. The risk of bias from included Randomized controlled trial (RCT) s was assessed using the Cochrane Collaboration's Tool. Newcastle-Ottawa Scale was employed to assess the included cohort's quality. The main outcomes of this review were treatment failure, mortality, intracranial pressure (ICP) reduction, and Cerebral Perfusion Pressure (CPP) increment. All the statistical analyses were performed using the Review Manager 5.4.1. A random-effects model was used to pool the studies when heterogeneity was seen, and the results were reported in the odds ratios (OR) and mean differences (MD) and the corresponding 95% confidence intervals.

Results: The results of the statistical study found that there was a significantly lower treatment failure rate [OR = 1.80 (1.26, 2.57); p = 0.001; I^2 = 74%], the lower mortality rate [OR = 2.17 (1.26, 3.73); p = 0.005; I^2 = 0%], a greater increase in CPP [MD = -1.28 (-2.50, -0.05); p = 0.04; I^2 = 0%] associated with hypertonic saline treatment as compared to mannitol treatment. However, concerning ICP decrease, there was no significant difference between the two treatment options [MD = 1.86 (-0.64, 4.36); p = 0.14; I^2 = 70%].

Conclusions: Quantitative and qualitative analysis of trials and observational studies comparing the efficacy of hypertonic saline and mannitol demonstrates that hypertonic saline is a preferable treatment option with greater effectiveness and safety than mannitol in managing patients with TBI.

Keywords: Hypertonic saline, mannitol, TBI, cerebral edema, systematic review, intracranial hypertension.

Introduction

Traumatic brain injury (TBI) is an accidental insult to brain tissue resulting from sudden mechanical trauma to the brain and can cause severe neurological morbidity and mortality [1]. Any apparent injury to the parenchyma of the brain that leads to the development of cerebral edema causes a progressive increase in ICP [2].

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Raised ICP concerns adverse events in patients with TBI, as uncontrolled or poorly controlled intracranial hypertension signifies a poor prognosis [3]. In patients with diffuse brain injury, any rise in ICP beyond 10 mm Hg heralds a poor neurological status with higher morbidity and mortality [4]. In addition to causing direct damage to the brain, raised ICP decreases CPP and cerebral blood flow [5,6]. A large fall in CPP can result in significant ischemic injury if autoregulation fails to maintain cerebral blood flow [7]. Following TBI, decreased cerebral blood flow resulting in ischemia is linked to a poor neurological prognosis and a greater mortality risk [8].

Management of patients with TBI and other types of brain injury requires frequent and careful ICP monitoring [9]. Prompt recognition with aggressive management of high ICP in the event of brain injury brings forth direct benefits on outcomes - more so when performed with a stepwise and individualized approach [10]. Aggressive medical therapy with emphasis on appropriate control of raised ICP can facilitate patients to make a better recovery without severe disability [11].

Effectual management of intracranial hypertension involves medical interventions such as Cerebrospinal fluid (CSF) drainage, sedation and osmotherapy, and avoidance of aggravating factors [12]. The use of barbiturates and steroids as a prophylactic measure and empiric therapy for raised ICP has proved ineffective, and definitive therapy should target the specific mechanisms leading to raised ICP, such as increased brain water content, increased cerebral blood volume, and CSF outflow resistance [13].

When administered, hypertonic fluids can reduce intracranial pressure and increase cerebral blood flow; the mechanism behind that is dehydrating cerebrovascular endothelium and erythrocytes. This can help minimize the secondary brain injury that follows head trauma [14]. Increasing the osmotic load by giving osmotic agents such as hypertonic saline, glycerol, and mannitol can effectively reduce ICP by pulling water from the brain tissue [15].

Mannitol lowers ICP by its immediate effect of plasma expansion which decreases blood viscosity, and by its slightly delayed osmotic effect of pulling out water from cerebral interstitial space [16]. It also tends to increase cerebral blood flow by reducing blood viscosity while constricting cerebral blood vessels and, thus, reducing ICP [17]. Hypertonic saline predominantly produces its effects by causing the osmotic transfer of fluid from the intracellular space to the interstitial and ultimately, to the intravascular space [18].

Literature reveals several research works that were conducted to compare the therapeutic efficacy and safety of mannitol and hypertonic saline. However, the generalizability of the findings of these studies is controversial and limited due to the different methodologies employed, small sample sizes, different potencies used, and different outcome measures. Our meta-analysis compared the efficacy of mannitol with hypertonic saline in patients with TBI. Data from all clinical trials and comparative studies were incorporated into our analysis.

Material and Methods

Eligibility criteria

Studies were included based on the described eligibility criteria using PICOS: P (Population); I (Intervention); C (Control); O (Outcome); S (Studies); only clinical trials and cohort studies published in English were selected. Studies conducted in hospitals full filling the inclusion criteria were used. Studies were chosen based on their primary or secondary outcome that matches our objective "treatment failure, mortality, CPP and ICP."

Search strategy and protocol registration

The Preferred Reporting Items for Systematic Review and Meta-analyses (PRISMA) guidelines were used to conduct our systematic review [19]. The search terms: "Saline Solution, Hypertonic," "mannitol," "cerebral edema," "intracranial hypertension or elevated ICP," "TBI," "Adult," and "children" were implemented; Medline database, Web of Science, and Google Scholar were employed for the literature search, from their inception to 13 October 2022. The protocol was registered on INPLASY which is the International Platform of Registered Systematic Review and Meta-analysis Protocols. The registration number is: INPLASY2022100010.

Study selection and data extraction

The investigators made use of electronic registers and databases. The searched studies were exported to the EndNote Reference Library software version 20.0.1 (Clarivate Analytics) to exclude duplicate articles. Data were retrieved using a spreadsheet program. The researchers came to an agreement on any discrepancies in the data.

Quality assessment of studies

The Cochrane Collaboration's Tool was used to evaluate the listed studies' possibility of bias. Three levels - high, unclear, and low - were used to classify the overall risk of bias in a judgment. Using the level of bias, the overall quality of risk was classified as having a high, moderate, or low risk of bias (Table 1). The Newcastle Ottawa Scale was used to assess the likelihood of bias in the included cohorts. Scores above 7 were labeled to have low bias risk, scores between 6-7 were labeled moderate bias risk, and scores between 1 and 5 were labeled to have high bias risk (Table 2).

Statistical analysis

Review Manager (version 5.4.1; Copenhagen: The Nordic Cochrane Center, The Cochrane Collaboration, 2020) was employed for all the statistical analysis. The data from included studies were pooled using the random-effects model, and the analysis was done by calculating the odds ratio (OR) with respective 95% confidence intervals (CI). To evaluate any differences between the subgroups chi-square test was performed. The sensitivity analysis was done to analyze the influence of any individual study in driving the results and assess the reasons for heterogeneity. According to Higgins and .Thompson [20], the scale for heterogeneity

Table 1. *Risk of bias of RCTs.*

Author and year	Adequate sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment	Incomplete outcome data	Selective outcome reporting	Other sources of Bias	Net risk
Battison et al. (2005) [21]	Low	Low	Low	High	Low	Low	Low	Low
Cottenceau et al. (2011) [22]	Low	Low	Low	Unclear	Low	Low	Low	Low
Harutjunyan et al. (2005) [23]	Low	Unclear	Unclear	Unclear	Low	Low	Low	Low
Huang et al. (2020) [24]	Unclear	Unclear	Unclear	Unclear	Low	Low	Low	Moderate
Jagannatha et al. (2016) [25]	Low	Unclear	Unclear	Unclear	Low	Low	Low	Low
Kumar et al. (2019) [27]	Low	Unclear	Unclear	Low	Low	Low	Low	Low
Patil and Gupta (2019) [29]	Low	Low	Low	Unclear	Low	Low	Low	Low
Vialet et al. (2003) [31]	Unclear	Unclear	High	Low	Low	Low	Low	Low

Table 2. *Quality assessment of cohort study.*

	Represent-ativeness of the exposed cohort	Selection of the Non-exposed cohort	Ascertainment of exposure	Demonstration that outcome of interest was not present at start of study	comparability of cohorts on the basis of the design or analysis	Assessment of outcome	Was follow-up long enough for outcomes to occur	Adequacy of follow-up of cohorts	Net score
Kerwin et al. (2009) [26]	1	1	1	1	1	1	1	1	8
Oddo et al. (2009) [28]	1	1	1	1	1	1	1	1	8
Vats et al. (1999) [30]	1	1	1	1	1	1	1	1	8
Yildizdas et al. (2005) [32]	1	1	1	1	1	1	1	1	8

was considered: I^2 = 25%-50% was considered moderate heterogeneity; 50%-75% as substantial heterogeneity; 75%-100% as considerable heterogeneity, and $p < 0.1$ indicated significant heterogeneity. A value of $p < 0.05$ was considered statistically significant for all analyses in our study.

Results

Literature search results

Initial results from a search of Medline database, Web of Science, and Google Scholar electronic databases revealed 732 relevant research. Following title and abstract-based exclusions, the full texts of 89 studies were reviewed for possible inclusion. There remained 12 studies for quantitative analysis (Figure 1).

Study characteristics

Table 3 shows the basic characteristics of included studies [21-32]. Among the 12 included studies, 8 studies are randomized controlled trials and 4 are cohort studies. The research was carried out in a variety of countries and areas all over the world. A total of six studies evaluated mortality outcomes, four studies evaluated treatment failure, seven studies evaluated the effect on raised ICP, and seven studies evaluated the effect on cerebral perfusion pressure. The studies encompass both the adult and pediatric populations.

Result of quality assessment

The funnel plot could not be used to assess publication as there were fewer than 10 studies.

Out of the 12 studies, 11 showed a low risk of bias [21-23,25-32], and only 1 study had a moderate risk of bias [24].

Results of meta-analysis

The detailed forest plots were used to outline the effect sizes of treatment failure rate, mortality outcome, ICP reduction, and CPP increment associated with hypertonic saline treatment compared to mannitol treatment (Figures 2-5).

Treatment failure of hypertonic saline compared to mannitol

Four studies reported data on treatment failure rates. The statistical analysis (Figure 2) showed a significantly lower treatment failure rate associated with hypertonic saline treatment compared to mannitol treatment [OR = 1.80 (1.26, 2.57); p = 0.001; I^2 = 74%].

Comparing the mortality reduction between hypertonic saline and mannitol

Six studies reported data on mortality outcomes. The statistical analysis (Figure 3) showed a significantly lower mortality rate in the hypertonic saline treatment group compared mannitol group [OR = 2.17 (1.26, 3.73); p = 0.005; I^2 = 0%].

The effect of hypertonic saline compared to mannitol on intracranial pressure

Seven studies reported data on ICP reduction. The statistical analysis (Figure 4) showed no significant

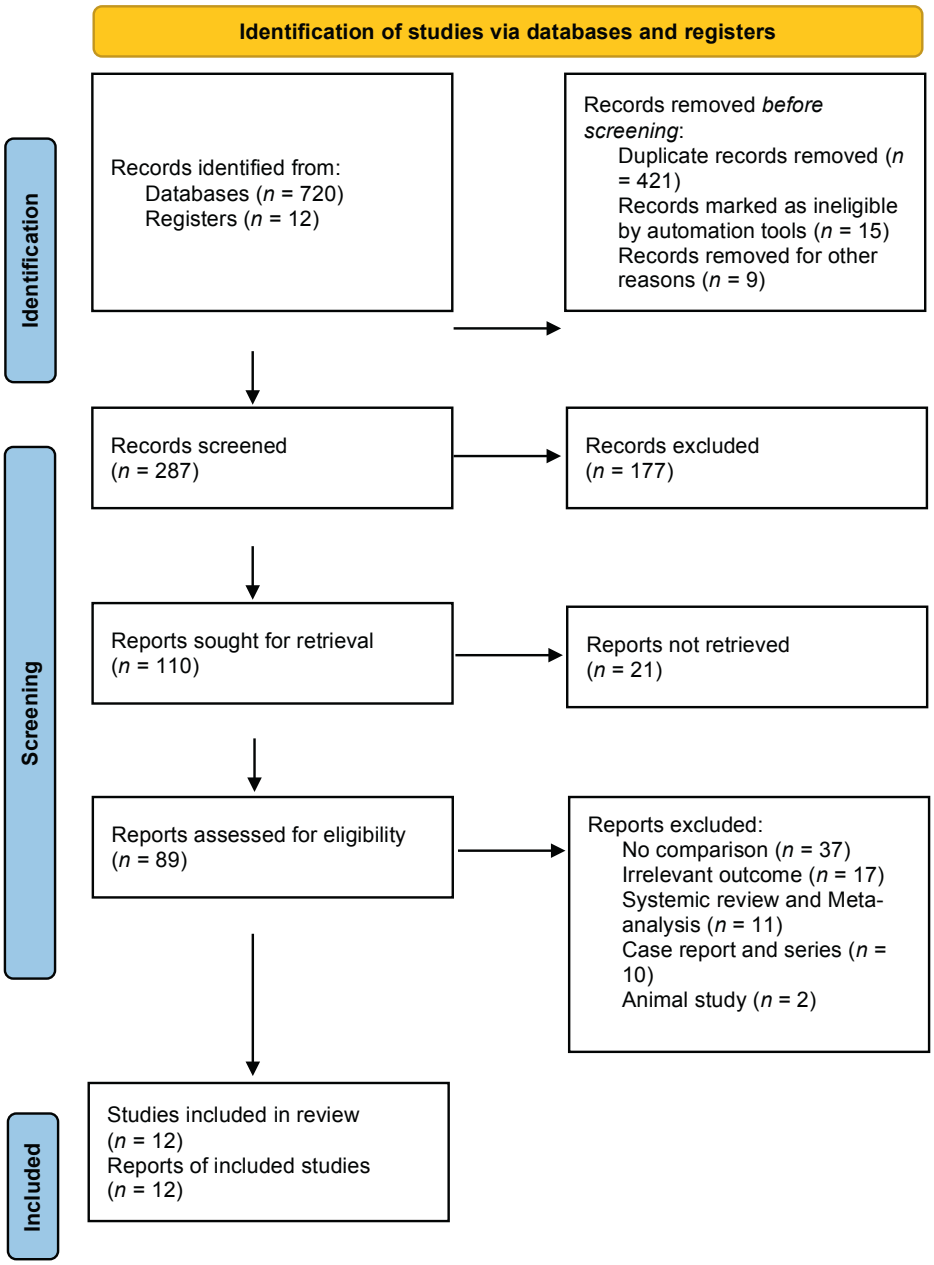

Figure 1. *PRISMA 2020 flow diagram for new systematic reviews which included searches of databases and registers only.*

difference in ICP reduction between hypertonic saline treatment and mannitol treatment [mean differences (MD) = 1.86 (-0.64, 4.36); $p = 0.14$; $I^2 = 70\%$].

The effect of hypertonic saline compared to mannitol on cerebral perfusion pressure

Seven studies reported data on CPP increment. The statistical analysis (Figure 5) showed that there was a significantly greater increase in CPP associated with hypertonic saline treatment as compared to mannitol treatment [MD = -1.28 (-2.50, -0.05); $p = 0.04$; $I^2 = 0\%$].

Sensitivity analysis

To determine how each study might affect the final result, a sensitivity analysis was performed. For the sensitivity analysis, the following method was employed: we excluded one study at a time, generating the OR and MD for the rest of the studies. No significant change was observed after excluding any individual study, the sensitivity analysis suggested that the results were robust.

Discussion

Our systematic review and meta-analysis of 12 published studies indicated that hypertonic saline is superior to mannitol in terms of CPP increase, treatment success, and mortality outcomes. In terms of ICP reduction, there is no substantial difference in the effectiveness of hypertonic saline and mannitol.

A study comparing the therapeutic efficacy of mannitol and hypertonic saline in treating raised ICP

Table 3. *Characteristics of included articles.*

Author and year	Study design	Study publication year	Study Location	Total patients (n)	Study population	Hypertonic saline infusions	Mannitol infusions	Risk of bias
Battison et al. (2005) [21]	RCT	2005	United King-dom	9	≥16 years old	9	9	Low
Cottenceau et al. (2011) [22]	RCT	2011	France, Israel	47	≥16 years old	22	25	Low
Harutjunyan et al. (2005) [23]	RCT	2005	Germany	32	>18 years	15	17	Low
Huang 2020 [24]	RCT	2020	China	83	≥18 years	236	221	Moderate
Jagannatha et al. (2016) [25]	RCT	2016	India	38	15-70 years	18	20	Low
Kerwin et al. (2009) [26]	Cohort	2009	United States	22	Mean age 35.7 years	108	102	Low
Kumar et al. (2019) [27]	RCT	2019	Germany	30	≤16 years	14	16	Low
Oddo et al. (2009) [28]	Cohort	2009	United States	12	Mean age 36 years	14	28	Low
Patil and Gupta (2019) [29]	RCT	2019	India	120	>18 years	40	40	Low
Vats et al. (1999) [30]	Cohort	1999	United States	43	Hypertonic sa-line (mean age 6.4 years) Mannitol (mean age 3.5 years)	82	56	Low
Vialet et al. (2003) [31]	RCT	2003	France	20	Hypertonic saline (mean age 35 years) Mannitol (mean age 30.8 years)	10	10	Low
Yildizdas et al. (2005) [32]	Cohort	2005	Turkey	67	Mean age 68.9 months	25	22	Low

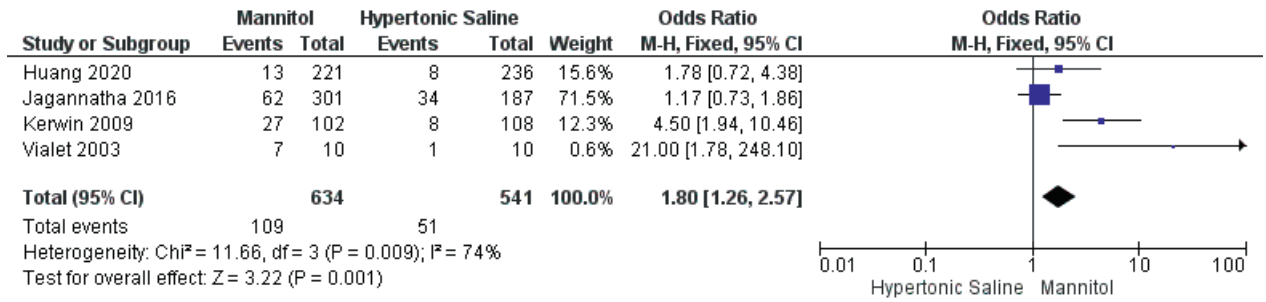

Figure 2. *Forest plot of treatment failure.*

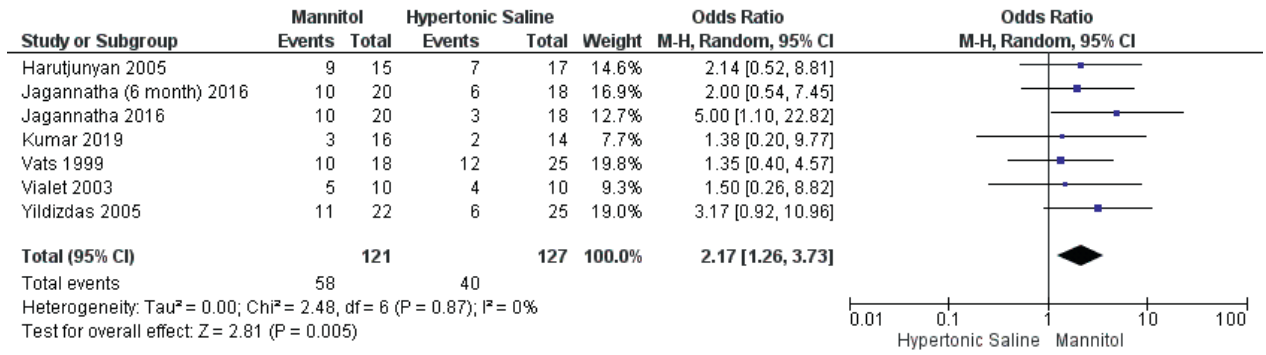

Figure 3. *Forest plot of mortality.*

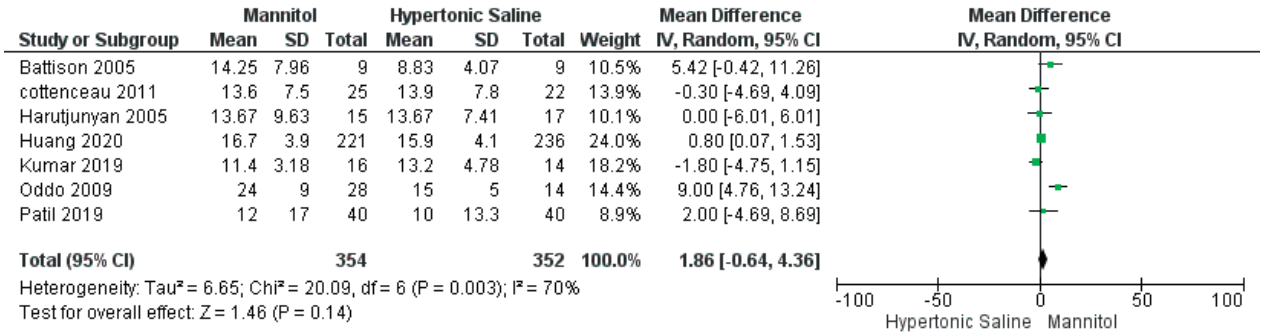

Figure 4. *Forest plot of ICP.*

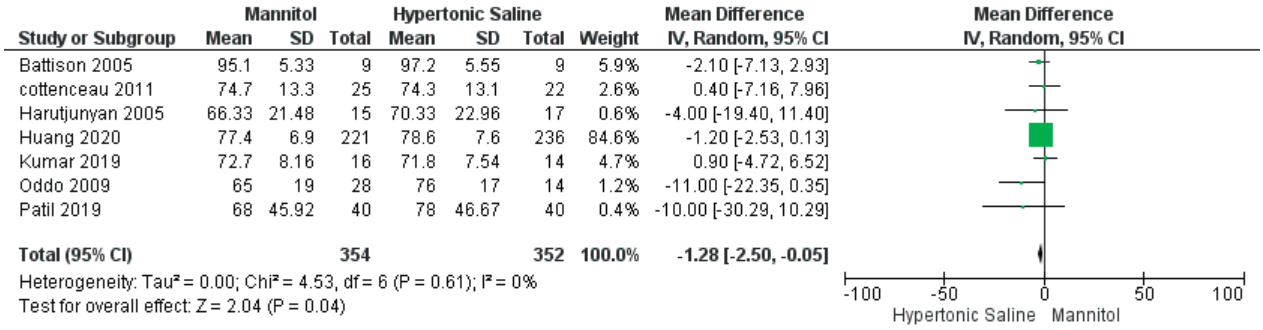

Figure 5. *Forest plot of CPP.*

associated with experimental intracerebral hemorrhage demonstrated that both interventions are equally effective, however, hypertonic saline may show a more prolonged effect [33]. Hypertonic saline has been found to be more effective than mannitol in treating refractory episodes of intracranial hypertension in severe cases of head trauma [31]. In an animal study comparing the therapeutic efficacy of mannitol and hypertonic saline/dextran solution, the initial ICP reduction with mannitol was found to be maintained for a longer duration while no difference in duration was observed after the subsequent administration of the drugs. Moreover, hypertonic saline/dextran was shown to impart greater CPP compared to mannitol by affecting the water content of the cerebral hemispheres [34].

Not only is the treatment with hypertonic saline superior to mannitol in the acute management of brain edema associated with brain injury, but repeated treatment with mannitol may also paradoxically aggravate the problem in some cases. It has been demonstrated that mannitol progressively accumulates in the brain tissue, and, with repeated administration, its concentration exceeds the plasma concentration. This reversal of the osmotic gradient between plasma and the edematous brain can potentially exacerbate vasogenic edema [35]. Moreover, osmotic diuresis with mannitol can induce apoptosis in vascular endothelial cells with the activation of various intracellular signaling pathways. This can directly produce detrimental effects on the vascular endothelium [36]. Mannitol may also disturb fluid and electrolyte balance which can override its beneficial effects and needs careful monitoring [37].

The superior benefit of hypertonic saline can also be inferred from the finding that repeated bolus administration of hypertonic saline can effectively reduce ICP in patients with raised ICP refractory to mannitol and barbiturates [38]. The effectiveness of hypertonic saline in reducing ICP and cerebral edema was found to be more pronounced in patients with head trauma and postoperative edema as compared to those with non-traumatic cerebral hemorrhage or cerebral infarction [39]. It has been demonstrated via case studies that intravenous hypertonic saline is a more effective treatment option with favorable outcomes when ICP reduction is required without diuresis in patients who have TBI [40].

Over and above that, resuscitation with hypertonic saline in the presence of concomitant hemorrhagic shock and head trauma can reduce cerebral edema while replenishing intravenous volume at the same time [41]. Such resuscitation can override the rise in ICP associated with fluid resuscitation by dehydrating areas of the brain with intact blood-brain barrier [42]. In addition to effectively reducing ICP in patients afflicted with severe brain injury, hypertonic saline also improves CPP and $PbtO_2$ [43].

Pooled data from clinical trials and observational studies showed that hypertonic saline is overall more effective than mannitol in the management of patients with TBI. Our research suggests that hypertonic saline is an effective and safe treatment for patients with TBI, and we propose that it be incorporated into current guidelines for the care of TBI patients.

Conclusions

Quantitative and qualitative analysis of trials and observational studies comparing the efficacy of hypertonic saline and mannitol demonstrates that hypertonic saline is a preferable treatment option with greater effectiveness and safety than mannitol in the management of patients with TBI.

Strength

Our article may be one of the few examples of research that has extensively assessed and compared the two osmotic treatments' effectiveness during the treatment of TBI. Data from trials and research carried out at numerous trauma centers across the world are given. Additionally, different quantities and potencies of mannitol and hypertonic saline have been assessed. We are the first to discuss the pediatric age group in research. Our findings thus offer more solid and thorough proof of the efficacy of these therapy choices.

Limitations

The generalizability of our study findings is limited in some ways. First, there is variability in the study designs. Second, the type of TBI experienced by patients, the concentration of osmotic solution infusion, and the duration and frequency of infusions are not uniform. Therefore, we were unable to make conclusive statements on the safest dose, concentration, and duration of infusion.

Conflict of interest

The authors declare that there is no conflict of interest regarding the publication of this article.

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Consent to participate

Not applicable.

Ethical approval

Not applicable.

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References

1. Capizzi A, Woo J, Verduzco-Gutierrez M. Traumatic brain injury: an overview of epidemiology, pathophysiology, and medical management. Med Clin North Am. 2020;104(2): 213–38. https://doi.org/10.1016/j.mcna.2019.11.001
2. Leinonen V, Vanninen R, Rauramaa T. Raised intracranial pressure and brain edema. Handb Clin Neurol. 2017;145:25–37. https://doi.org/10.1016/B978-0-12-802395-2.00004-3
3. Signorini DF, Andrews PJ, Jones PA, Wardlaw JM, Miller JD. Adding insult to injury: the prognostic value of early secondary insults for survival after traumatic brain injury. J Neurol Neurosurg Psychiatry. 1999;66(1):26–31. https://doi.org/10.1136/jnnp.66.1.26
4. Miller JD, Becker DP, Ward JD, Sullivan HG, Adams WE, Rosner MJ. Significance of intracranial hypertension in severe head injury. J Neurosurg. 1977;47(4):503–16. https://doi.org/10.3171/jns.1977.47.4.0503
5. Marmarou A, Saad A, Aygok G, Rigsbee M. Contribution of raised ICP and hypotension to CPP reduction in severe brain injury: correlation to outcome. Acta Neurochir Suppl (Wien). 2005;95:277–80. https://doi.org/10.1007/3-211-32318-X_57
6. Fortune JB, Feustel PJ, Graca L, Hasselbarth J, Kuehler DH. Effect of hyperventilation, mannitol, and ventriculostomy drainage on cerebral blood flow after head injury. J Trauma. 1995;39(6):1091–7. https://doi.org/10.1097/00005373-199512000-00014
7. Claassen JA, Thijssen DH, Panerai RB, Faraci FM. Regulation of cerebral blood flow in humans: physiology and clinical implications of autoregulation. Physiol Rev. 2021;101(4):1487–559. https://doi.org/10.1152/physrev.00022.2020
8. Bouma GJ, Muizelaar JP, Choi SC, Newlon PG, Young HF. Cerebral circulation and metabolism after severe traumatic brain injury: the elusive role of ischemia. J Neurosurg. 1991;75(5):685–93. https://doi.org/10.3171/jns.1991.75.5.0685
9. Kawoos U, McCarron RM, Auker CR, Chavko M. Advances in intracranial pressure monitoring and its significance in managing traumatic brain injury. Int J Mol Sci. 2015;16(12):28979–97. https://doi.org/10.3390/ijms161226146
10. Tripathy S, Ahmad SR. Raised intracranial pressure syndrome: a stepwise approach. Indian J Crit Care Med. 2019;23(S2 Suppl 2):S129–35. https://doi.org/10.5005/jp-journals-10071-23190
11. Becker DP, Miller JD, Ward JD, Greenberg RP, Young HF, Sakalas R. The outcome from severe head injury with early diagnosis and intensive management. J Neurosurg. 1977;47(4):491–502. https://doi.org/10.3171/jns.1977.47.4.0491
12. Rangel-Castilla L, Gopinath S, Robertson CS. Management of intracranial hypertension. Neurol Clin. 2008;26(2):521–41, x. Erratum in: Neurol Clin. 2008;26(3):xvii. https://doi.org/10.1016/j.ncl.2008.02.003
13. Miller JD, Piper IR, Dearden NM. Management of intracranial hypertension in head injury: matching treatment with cause. Acta Neurochir Suppl (Wien). 1993;57:152–9. https://doi.org/10.1007/978-3-7091-9266-5_22
14. Shackford SR, Zhuang J, Schmoker J. Intravenous fluid tonicity: effect on intracranial pressure, cerebral blood flow, and cerebral oxygen delivery in focal brain injury. J Neurosurg. 1992;76(1):91–8. https://doi.org/10.3171/jns.1992.76.1.0091

15. Jha SK. Cerebral edema and its management. Med J Armed Forces India. 2003;59(4):326–1. https://doi.org/10.1016/S0377-1237(03)80147-8

16. Shawkat H, Westwood MM, Mortimer A. Mannitol: a review of its clinical uses. Contin Educ Anaesth Crit Care Pain. 2012;12(2):82–5. https://doi.org/10.1093/bjaceaccp/mkr063

17. Muizelaar JP, Wei EP, Kontos HA, Becker DP. Mannitol causes compensatory cerebral vasoconstriction and vasodilation in response to blood viscosity changes. J Neurosurg. 1983;59(5):822–8. https://doi.org/10.3171/jns.1983.59.5.0822

18. Strandvik GF. Hypertonic saline in critical care: a review of the literature and guidelines for use in hypotensive states and raised intracranial pressure. Anaesthesia. 2009;64(9):990–1003. https://doi.org/10.1111/j.1365-2044.2009.05986.x

19. Hutton B, Salanti G, Caldwell DM, Chaimani A, Schmid CH, Cameron C, et al. The PRISMA extension statement for reporting of systematic reviews incorporating network meta-analyses of health care interventions: checklist and explanations. Ann Intern Med. 2015;162(11):777–84. https://doi.org/10.7326/M14-2385

20. Higgins JPT, Thompson SG. Quantifying heterogeneity in a meta-analysis. Stat Med. 2002;21:1539–58.

21. Battison C, Andrews PJ, Graham C, Petty T. Randomized, controlled trial on the effect of a 20% mannitol solution and a 7.5% saline/6% dextran solution on increased intracranial pressure after brain injury. Crit Care Med. 2005;33(1):196–202. https://doi.org/10.1097/01.CCM.0000150269.65485.A6

22. Cottenceau V, Masson F, Mahamid E, Petit L, Shik V, Sztark F, et al. Comparison of effects of equiosmolar doses of mannitol and hypertonic saline on cerebral blood flow and metabolism in traumatic brain injury. J Neurotrauma. 2011;28(10):2003–12. https://doi.org/10.1089/neu.2011.1929

23. 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. Crit Care. 2005;9(5):R530–40.

24. Huang X, Yang L, Ye J, He S, Wang B. Equimolar doses of hypertonic agents (saline or mannitol) in the treatment of intracranial hypertension after severe traumatic brain injury. Randomized controlled trial. Medicine (Baltimore). 2020;99(38):e22004. https://doi.org/10.1097/MD.0000000000022004

25. Jagannatha AT, Sriganesh K, Devi BI, Rao GS. An equiosmolar study on early intracranial physiology and long term outcome in severe traumatic brain injury comparing mannitol and hypertonic saline. J Clin Neurosci. 2016;27:68–73. https://doi.org/10.1016/j.jocn.2015.08.035

26. Kerwin AJ, Schinco MA, Tepas JJ, Renfro WH, Vitarbo EA, Muehlberger M. The use of 23.4% hypertonic saline for the management of elevated intracranial pressure in patients with severe traumatic brain injury: a pilot study. J Trauma. 2009;67(2):277–82. https://doi.org/10.1097/TA.0b013e3181acc726

27. Kumar SA, Devi BI, Reddy M, Shukla D. Comparison of equiosmolar dose of hyperosmolar agents in reducing intracranial pressure-a randomized control study in pediatric traumatic brain injury. Childs Nerv Syst. 2019;35(6):999–1005. https://doi.org/10.1007/s00381-019-04121-3

28. Oddo M, Levine JM, Frangos S, Carrera E, Maloney-Wilensky E, Pascual JL, et al. Effect of mannitol and hypertonic saline on cerebral oxygenation in patients with severe traumatic brain injury and refractory intracranial hypertension. J Neurol Neurosurg Psychiatry. 2009;80(8):916–20. https://doi.org/10.1136/jnnp.2008.156596

29. Patil H, Gupta R. A comparative study of bolus dose of hypertonic saline, mannitol, and mannitol plus glycerol combination in patients with severe traumatic brain injury. World Neurosurg. 2019;125:e221–8. https://doi.org/10.1016/j.wneu.2019.01.051

30. Vats A, Chambliss CR, Anand KJ, Pettignano R. Is hypertonic saline an effective alternative to mannitol in the treatment of elevated intracranial pressure in pediatric patients? J Intensive Care Med. 1999;14(4):184–8. https://doi.org/10.1177/088506669901400403

31. Vialet R, Albanèse J, Thomachot L, Antonini F, Bourgouin A, Alliez B, et al. 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. Crit Care Med. 2003;31(6):1683–7. https://doi.org/10.1097/01.CCM.0000063268.91710.DF

32. Yildizdas D, Altunbasak S, Celik U, Herguner O. Hypertonic saline treatment in children with cerebral edema. Indian Pediatr. 2006;43(9):771–9.

33. Qureshi AI, Wilson DA, Traystman RJ. Treatment of elevated intracranial pressure in experimental intracerebral hemorrhage: comparison between mannitol and hypertonic saline. Neurosurgery. 1999;44(5):1055–63. https://doi.org/10.1097/00006123-199905000-00064

34. Berger S, Schürer L, Härtl R, Deisböck T, Dautermann C, Murr R, et al. 7.2% NaCl/10% dextran 60 versus 20% mannitol for treatment of intracranial hypertension. Acta Neurochir Suppl (Wien). 1994;60:494–8. https://doi.org/10.1007/978-3-7091-9334-1_135

35. Kaufmann AM, Cardoso ER. Aggravation of vasogenic cerebral edema by multiple-dose mannitol. J Neurosurg. 1992;77(4):584–9. https://doi.org/10.3171/jns.1992.77.4.0584

36. Malek AM, Goss GG, Jiang L, Izumo S, Alper SL. Mannitol at clinical concentrations activates multiple signaling pathways and induces apoptosis in endothelial cells. Stroke. 1998;29(12):2631–40. https://doi.org/10.1161/01.STR.29.12.2631

37. Czupryna P, Moniuszko-Malinowska A, Grygorczuk S, Pancewicz S, Dunaj J, Król M, et al. Effect of a single dose of mannitol on hydration status and electrolyte concentrations in patients with tick-borne encephalitis. J Int Med Res. 2018;46(12):5083–9. https://doi.org/10.1177/0300060518790175

38. Horn P, Münch E, Vajkoczy P, Herrmann P, Quintel M, Schilling L, et al. Hypertonic saline solution for control of elevated intracranial pressure in patients with exhausted response to mannitol and barbiturates. Neurol Res. 1999;21(8):758–64. https://doi.org/10.1080/01616412.1999.11741010

39. Qureshi AI, Suarez JI, Bhardwaj A, Mirski M, Schnitzer MS, Hanley DF, et al. Use of hypertonic (3%) saline/acetate infusion in the treatment of cerebral edema: effect on intracranial pressure and lateral displacement of the brain. Crit Care Med. 1998;26(3):440–6. https://doi.org/10.1097/00003246-199803000-00011

40. Worthley LI, Cooper DJ, Jones N. Treatment of resistant intracranial hypertension with hypertonic saline. Report of two cases. J Neurosurg. 1988;68(3):478–81. https://doi.org/10.3171/jns.1988.68.3.0478

41. Wisner DH, Schuster L, Quinn C. Hypertonic saline resuscitation of head injury: effects on cerebral water content. J Trauma. 1990;30(1):75–8. https://doi.org/10.1097/00005373-199001000-00011

42. Battistella FD, Wisner DH. Combined hemorrhagic shock and head injury: effects of hypertonic saline (7.5%) resuscitation. J Trauma. 1991;31(2):182–8. https://doi.org/10.1097/00005373-199102000-00005

43. Rockswold GL, Solid CA, Paredes-Andrade E, Rockswold SB, Jancik JT, Quickel RR. Hypertonic saline and its effect on intracranial pressure, cerebral perfusion pressure, and brain tissue oxygen [s]. Neurosurgery. 2009;65(6):1035–41. https://doi.org/10.1227/01.NEU.0000359533.16214.04