To compare the effects of hypertonic saline and mannitol for treatment of adults with elevated intracranial pressure: a systematic review and meta-analysis of randomized controlled trails

Cheng Peng[1], Fan Gao[1], Lei Zhang[1], Wei Rao[1], Baohai Feng[1], Jiangning Lv[1], Qiang Hao[1], Yangang Wang[1], and Yuanli Zhao[1]

[1]Affiliation not available

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Abstract

Aims: Currently, mannitol and hypertonic saline (HTS) are mostly used in treatment of adult with elevated intracranial pressure (ICP). However, there is no high-level evidence on the superiority of mannitol versus HTS. Therefore, a systematic review and meta-analysis was performed to compare effects of hypertonic saline and mannitol for treatment of adults with elevated ICP. Methods: We performed a search on lots of databases for eligible studies. Prospective randomized control trials comparing HTS and mannitol in adults with elevated ICP were included, and ICP monitoring should be applied. Primary outcome was change of ICP values, and secondary outcomes were changes of cerebral perfusion pressure (CPP), mean arterial pressure (MAP), heart rate, serum sodium, serum osmolarity and hematocrit (HCT). Results: A total of ten studies (384 patients, 1578 episodes) were included. A pooled result indicated HTS reduced ICP more effectively than mannitol. At 0.5 h, 1 h, and 2 h after intervention, results also showed a better efficiency of HTS than mannitol. In addition, results indicated elevation of CPP, serum sodium and serum osmolarity were all more in HTS group than in mannitol group. And there were no statistical significance in changes of MAP, HCT and HR between the two interventions. Conclusion: Our study indicated HTS had a better efficiency in reduction of elevated ICP than mannitol in earlier stage. Based on the current level of evidence of ICP control and effects in other physiological indicators, HTS could be recommended as a first-line agent for managing patients with elevated ICP.

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Cheng Peng[a, b], Fan Gao[b], Lei Zhang[c], Wei Rao[d], BaoHai Feng[b], Jiangning Lv[b], Qiang Hao[a], Yangang Wang[c], Yuanli Zhao[a]

[a] Department of Neurosurgery, Beijing Tiantan Hospital, Capital Medical University,

[b] The 984 Hospital of Chinese People's Liberation Army, Beijing 100094, China

[c] Department of Neurosurgery, Xijing Hospital, Fourth Military Medical University, Xi'an, Shaanxi 710032, P.R. China

[d] Department of Neurosurgery, The sixth Medical Center of Chinese People's Liberation Army General Hospital, Beijing, China

Corresponding author : Yuanli Zhao, Department of Neurosurgery, Beijing Tiantan Hospital, Capital Medical University, Email:*zhaoyuanli@126.com*

Cheng Peng (doctorpc@163.com) and Fan Gao contributed equally to this work.

Abstract

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Methods : We performed a search on lots of databases for eligible studies. Prospective randomized control trials comparing HTS and mannitol in adults with elevated ICP were included, and ICP monitoring should be applied. Primary outcome was change of ICP values, and secondary outcomes were changes of cerebral perfusion pressure (CPP), mean arterial pressure (MAP), heart rate, serum sodium, serum osmolarity and hematocrit (HCT).

Results: A total of ten studies (384 patients, 1578 episodes) were included. A pooled result indicated HTS reduced ICP more effectively than mannitol. At 0.5 h, 1 h, and 2 h after intervention, results also showed a better efficiency of HTS than mannitol. In addition, results indicated elevation of CPP, serum sodium and serum osmolarity were all more in HTS group than in mannitol group. And there were no statistical significance in changes of MAP, HCT and HR between the two interventions.

Conclusion: Our study indicated HTS had a better efficiency in reduction of elevated ICP than mannitol in earlier stage. Based on the current level of evidence of ICP control and effects in other physiological indicators, HTS could be recommended as a first-line agent for managing patients with elevated ICP.

Key words: intracranial pressure, mannitol, hypertonic saline, meta-analysis, systematic review.

Introduction

Acutely elevated intracranial pressure (ICP) is a life-threatening neurosurgical emergency situation, which is a frequent manifestation of several brain injury in case of traumatic brain injury (TBI), subarachnoid hemorrhage (SAH), stroke (hemorrhagic and ischemic), infection, and neoplasm. The secondary brain injury associated with elevated ICP can lead to impaired cerebral perfusion pressure (CPP) and poor neurological outcome and mortality (1). And the normalization of ICP in patients with brain injury is assumed to limit secondary brain injury and improve outcome. In conditions of elevated ICP, hyperosmolar agent is used as the most common treatment. And mannitol and hypertonic saline (HTS) are usually employed for reduction of elevated ICP in clinical treatment. Mannitol is a typical medicine, which plays an important role in treatment of elevated ICP for about 60 years. For recent years, HTS (concentrations ranging from 3% to 30%) has been emerging as a good substitute for mannitol. Several studies suggested that HTS was better than mannitol in controlling elevated ICP (2, 3). However, some other studies reported that there was no difference between HTS and mannitol in reduction of ICP (4-7). Moreover, the "Guidelines for the Management of Severe Traumatic Brain Injury (Fourth Edition)" stated "although hyperosmolar therapy may lower intracranial pressure, there was insufficient evidence about effects on clinical outcomes to support a specific recommendation, or to support use of any specific hyperosmolar agent" (8).

Although there were some similar published systematic reviews and meta-analyses, the methodological quality and the conclusions were not satisfactory and rigorous. Up to now, there is no high-level evidence on the superiority of mannitol versus HTS in reducing ICP or improving outcomes. After searching electric databases, we found several high quality and eligible trials. Consequently, we combined their findings in a new meta-analysis to explore a more precise conclusion. In present article, we analyzed and summarized previous meta-analyses. Then, by searching electric databases and screening numerous articles, the eligible trials and quantitative data were extracted. Finally, a systematic review and meta-analysis was performed to compare the effects of HTS and mannitol in treatment of adults with elevated ICP. Furthermore, we expect present conclusions would give several valuable strategies for clinical treatment.

Methods

2.1. Search strategy and study selection

We registered our review in PROSPERO, and registration ID is CRD42021225236. We performed a search on

PubMed, EMBASE, Cochrane Library, Web of Science, and ClinicalTrials.gov databases for eligible studies. We used OpenGrey and National Technical Information Service databases to search relevant grey literature. The text words or MeSH were "randomized controlled trail" "intracranial pressure", "elevated intracranial pressure", "hyperosmolar agent", "hypertonic saline", "mannitol" and other synonymous free text words and phrases were substituted for searching comprehensively. We did not restrict studies based on language and status of publication. And the published date was restricted from 2000 to now. We also searched previous published similar meta-analysis, and screened the included studies. The search was completed by two investigators independently. And all disagreements were determined by a third investigator. Then there were three independent investigators reviewed all references and screened out eligible studies which conformed to the inclusion and exclusion criteria. And all disagreements were determined by a fourth investigator.

2.2. Inclusion criteria :

The included literatures should meet the following items: Patients: (1) Adult ([?] 16 years old, and of both sexes), (2) episodes of elevated ICP occurred when used osmotic agents, (3) ICP monitoring (undergoing quantitative ICP measurement). Interventions: treatments included both HTS and mannitol. Outcomes: the available quantitative data of ICP. Study: randomized controlled trails, full text available.

Exclusion criteria :

Studies met the following criteria were excluded: (1) No threshold value of ICP when osmotic agents were used. (2) Patients with liver or renal failure, cardiac dysfunction, hypovolemic shock, or multiple organ failure. (3) Qualitative trials, which had no exact ICP values. (4) Prehospital studies. (5) Animal studies, retrospective studies, cohort studies, case report, meta-analysis, and reviews.

Data extraction

To reduce bias, two independent authors extracted data from included studies. And another author checked the consistencies of the two sets of data. If there were disagreements, the final decisions were made by discussion. The basic information included the followings: first author's name, publication date, study design, country, sample size, interventions. Furthermore, the screened clinical outcomes of interest as followings: (1) ICP, (2) CPP, (3) heart rate (HR), (4) mean arterial pressure (MAP), (5) serum sodium, (6) serum osmolarity, (7) hematocrit (HCT). Several interested data were missing, and we had contacted the corresponding authors to get the information.

Risk of bias

Three authors assessed risk of bias of included studies independently. Another author solved inconsistencies, if necessary. The Cochrane tool framework was used to assess risk of bias (9). Mainly included the following items: (1) random sequence generation (selection); (2) allocation concealment (selection bias); (3) blinding of participants and personal (performance bias); (4) blinding of outcomes assessment (detection bias); (5) incomplete outcome data (attrition bias); (6) selective reporting (reporting bias); (7) Other bias. For each item, we assessed the risk of bias as "low risk", "high risk" or "unclear". And we generated a risk of bias summary figure upon completion of these assessment.

Statistical analysis

Although data in different articles were defined variably, we changed them in a unified form by the Cochrane Handbook (10). Not every extracted outcomes could be analyzed meaningfully, we only performed meta-analyses if outcomes were investigated by at least 3 RCTs. The continuous variables were pooled using the mean differences (MD) and 95% confidence interval (Cl). The heterogeneity of the studies was assessed by Q test ($P < 0.10$ as regards for significant heterogeneity) and I^2 statistic (I^2= 0%-25%, no heterogeneity; I^2 = 25%-50%, moderate heterogeneity; I^2 = 50%-75%, large heterogeneity; I^2 = 75%-100% extreme heterogeneity) (11). A random-effect model was applied when $I^2 > 50\%$, otherwise fix-effect model was applied. We performed a sensitivity analysis by excluding each study in turn for outcomes to investigate the potential source of heterogeneity and effect of each study on pooled results. And publication bias was estimated by a

contour-enhanced funnel plot and Egger's test. All data were analyzing by Review Manager 5.3 and STATA 16.

Characteristics and conclusions of similar systematic reviews and meta-analyses

We searched and selected similar systematic reviews and meta-analyses on PubMed, EMBASE, Cochrane Library, Web of Science, and ClinicalTrials.gov databases. And key information and conclusions were extracted for further analysis. For methodological quality evaluation, the AMSTAR 2 (A MeaSurement Tool to Assess systematic Reviews 2) assessment tool was used. AMSTAR 2 consists of 16 items (7 critical domains: item 2, 4, 7, 9, 11, 13, 15), graded as "Yes," "Partial Yes," and "No" (12). Rating overall confidence in the results of reviews is as follows: "Critically low", "Low", "Moderate" and "High" (12). Three independent authors evaluated the 16 items and rated all reviews. And the inconsistencies were discussed by all three authors.

Results

3.1. Literature search and characteristics of included studies

As shown in Fig 1, our literature search covers 2257 articles. The remaining 1814 studies were reviewed through skimming title and abstract after eliminating duplicates. Then, 69 articles were screened out for further full-text reading. After reading, we excluded 59 studies which did not confirm to inclusion criteria. Finally, 10 studies were selected for further meta-analysis.

Ten studies with a total of 384 patients (1578 episodes) were covered in this systematic review and meta-analysis. In each study, the demographic characteristics of the two groups were similar. And the characteristics of qualified studies are summarized in Table 1. Six studies defined any spontaneous ICP increase to >20 mmHg as an independent elevated ICP episode, then started mannitol or HTS treatment and recorded changes of ICP (2, 4, 5, 13-15). In these studies, total number of episodes were considered as final sample size. And the number of patient was considered as sample size in other four studies which did not define elevated ICP episodes. Therefore, the sample size ranged from 20 to 488. There were three groups in study of Patil, H. and Ichai, C., and the interested data only from mannitol group and HTS group which were extracted (13, 16). In all included trials, HTS solutions ranging in concentrations from 3% to 15% were compared with 15% or 20% mannitol.

3.2. Risk of bias

Results of risk of bias are showed in Figure 2. For random sequence generation, three studies which reported use a computer generated randomization sequence and sealed envelopes, were considered as low risk of bias (2, 6, 13). One study was considered as high risk of bias because of no exact grouping in trial (5). And others did not referred to exact methods, which were considered as unclear of bias. Six studies used sealed envelope method of randomization, random code generated by computer and a card-selection system to assess allocation concealment, and these studies were considered as low risk of bias. Other four studies were considered high risk of bias (4, 5, 13, 15). Because in these studies, the treatment were performed crosswise. Because of different volumes of two treatments, there were 2 studies consider as high risk of performance bias (7, 14). And there were two studies were considered as low risk of detection bias (4, 5). Others were not referred to detection methods, which were considered as unclear of bias. And all studies had no incomplete outcome data and no selective reporting, which were low risk of reporting bias.

Reduction of ICP

Clinically, HTS and mannitol are usually given as a bolus therapy. And the onset action of mannitol and HTS on ICP begin within minutes, and duration of both are to 6 h - 8 h (17). Therefore the detecting time point would not be too long. In eligible trials, interested data of changes of ICP were at baseline and after treatment. However, time points in included studies were not very coincident. In that case, the first reported records of ICP changes were extracted for general meta-analysis. The time point of first recorded change of ICP was o.5 h in seven studies (4, 6, 7, 13, 15, 16, 18), 1 h in one study (14), day 1 in one study (2) and

the last study only reported the maximum reduction of ICP (5). In general meta-analysis of ICP reduction, a fixed-effect model was applied because of low heterogeneity ($p = 0.93$, $I^2 = 0\%$, no heterogeneity). The pooled mean of ICP reduction, comparing HTS to mannitol, was 0.76 mm Hg (95% CI: 0.44 to 1.08, $p < 0.00001$). Results indicated that HTS was more effective than mannitol for reduction of elevated ICP in the general meta-analysis (Fig 3).

Moreover, there were other reported time points of ICP reduction in eligible studies. Therefore, for a more precise result, we performed meta-analyses based on reduction of ICP at different time points (Fig 4). Seven studies provided complete ICP data at baseline and 0.5 h after intervention (4, 6, 7, 13, 15, 16, 18). A fixed-effect model was applied (0.5 h subgroup, $p = 0.87$, $I^2 = 0\%$, no heterogeneity), and the pooled results showed mean of ICP reduction, comparing HTS to mannitol, was 0.74 mm Hg (95% CI: 0.41 to 1.07, $p < 0.0001$). Six studies reported complete ICP data at baseline and 1 h after intervention (4, 7, 13, 14, 16, 18). Then a fixed-effect model was applied (1 h subgroup, $p = 0.10$, $I^2 = 46\%$, moderate heterogeneity), and the pooled results showed mean of ICP reduction, comparing HTS to mannitol, was 1.60 mm Hg (95% CI: 0.77 to 2.44, $p = 0.0002$). Four studies provided complete ICP data at baseline and 2 h after intervention (4, 6, 7, 13). In 2 h subgroup, a random-effect model was applied ($p = 0.05$, $I^2 = 62\%$, large heterogeneity), and the pooled results showed mean of ICP reduction, comparing HTS to mannitol, was 1.50 mm Hg (95% CI: 0.15 to 2.85, $p = 0.03$). Based on data from included studies, only data at 0.5 h, 1 h and 2 h were eligible for meta-analysis. And all results indicated that HTS was more effective than mannitol in reducing elevated ICP in earlier stage.

Change of secondary outcomes

Also, some studies reported changes of CPP, MAP, serum sodium, serum osmolarity, HCT and HR after intervening with mannitol or HTS. As limitation, eligible data extracted for meta-analysis were from baseline and time of first record after treatment.

Changes of CPP were reported in eight studies, and a random-effect model was applied ($p < 0.00001$, $I^2 = 88\%$, extreme heterogeneity). The pooled results showed mean of CPP elevation, comparing HTS to mannitol, was 5.02 mm Hg (95% CI: 1.09 to 8.95, $p = 0.01$) (Fig 5) (2, 4, 6, 13-16, 18). Seven studies reported changes of serum sodium (2, 4, 6, 7, 14-16). A random-effect model was applied ($p < 0.00001$, $I^2 = 96\%$, extreme heterogeneity), and the pooled results showed mean of serum sodium elevation, comparing HTS to mannitol, was 6.51 mmol/L (95% CI: 3.23 to 9.79, $p < 0.0001$) (Fig 5). Changes of serum osmolarity were reported in six studies (2, 4, 14-16, 18). A random-effect model was applied ($p < 0.00001$, $I^2 = 92\%$, extreme heterogeneity), and the pooled results showed mean of serum sodium elevation, comparing HTS to mannitol, was 8.22 mOsm/kg (95% CI: 2.92 to 13.52, $p = 0.002$) (Fig 5). Pooled results indicated that elevation of CPP, serum sodium and serum osmolarity were all more in HTS group than in mannitol group in treatment of elevated ICP.

As for MAP, there were seven studies reported the changes (2, 4, 6, 14-16, 18). A random-effect model was applied ($p < 0.00001$, $I^2 = 90\%$, extreme heterogeneity), and the pooled results showed mean of MAP elevation, comparing HTS to mannitol, was 1.86 mm Hg (95% CI: -1.73 to 5.44, $p = 0.31$) (Fig 5). Changes of HCT were reported only in three studies (6, 16, 18). A fixed-effect model was applied ($p = 0.31$, $I^2 = 15\%$, no heterogeneity), and the pooled results showed mean of HCT change, comparing HTS to mannitol, was -0.21 (95% CI: -1.59 to 1.17, $p = 0.76$) (Fig 5). Three studies referred to outcomes of change of HR (2, 16, 18). A fixed-effect model was applied ($p = 0.32$, $I^2 = 13\%$, no heterogeneity), and the pooled results showed mean of HR change, comparing HTS to mannitol, was 1.4 beats/minute (95% CI: -1.00 to 3.80, $p = 0.25$) (Fig 5). These pooled results demonstrated that there was no statistical significance in change of MAP, HCT and HR between two interventions.

Sensitivity analysis

Sensitivity analysis was performed for present meta-analyses by removing each study in turn and reran a new meta-analysis. In meta-analysis groups of ICP-general, ICP-0.5 h, CPP, serum sodium, serum osmolarity, remained pooled results were not significantly altered, which indicated our results were stable and receivable.

Because of limited studies, sensitivity analysis were not performed in meta-analyses of ICP-2 h, HCT, and HR. However, in meta-analysis of MAP, after removing study of Huang Xue 2015 or Patil, H 2019, pooled results were changed respectively (0.00 mm Hg (95% CI: -1.11 to 1.11, p = 1.00) p = < 0.0001, I^2 = 83%; 0.78 mm Hg (95% CI: -0.26 to 1.83, p = 0.14) p = < 0.00001, I^2 = 89%) (4, 16). Moreover, in ICP-1 h meta-analysis, pooled results changed to 1.80 mm Hg (95% CI: 0.95 to 2.65, p < 0.0001) p = 0.61, I^2 = 0%, when removing study of Francony, G. 2008 (7).

Publication bias

Results of contour-enhanced funnel plot showed there was only one imputed study (Fig 6). And results of mean difference in observed group and observed + imputed group were not significant difference (0.761 vs 0.775) (S 1). Therefore, there was no evident publication bias. In addition, results of Egger's test (P > 0.7481) suggested an absence of publication bias as well (S 2).

Reviewed and summarized previous similar systematic reviews and meta-analyses

In addition, we summarized and extracted some main items and conclusions of previous similar systematic reviews and meta-analyses (Table 2). Results showed that there were seven studies about the similar subject. Three of them demonstrated HTS was more effective than mannitol for treatment of elevated ICP (19-21). The other four studies indicated there was no significant difference between HTS and mannitol in ICP reduction (22-25). As rating by AMSTAR 2, only one studies was rated as "Moderate" (24), even there were three rated "Critical Low" (S 3) (19, 20, 25). Results of methodological evaluation by AMSTAR 2 demonstrated that all previous studies might not have high qualities, and the confidence was deficient.

Disscussion

In present systematic review and meta-analysis, for a meticulous result, not only a general meta-analysis but also analyses of different time points were performed. Finally, a conclusion was drew that HTS was more effective than mannitol for reduction of elevated ICP in earlier stage (0.5 h, 1.0 h, and 2 h). And the high quality review was performed on the basis of AMSTAR 2. Of note, although results of heterogeneity showed that ICP could be ignored in respective analysis, we still preformed sensitivity analysis to show credibility and stability. Finally, all results preferred the efficacy of HTS more than mannitol.

As aforementioned, we researched and summarized seven previous similar meta-analyses. The final conclusions about treatment with HTS or mannitol in reduction of elevated ICP were always vary and the problem which was the most proper approach remained controversial. The heterogeneous results were not surprising given methodological differences, including various definitions of ICP treatment thresholds and treatment failure thresholds, sampling time to determine ICP change, formulation and osmolar loads of solutions, and diverse study populations. Although there are several imperfect details in these studies, previous meta-analyses are worth leaning and of great significance.

It was demonstrated that recommended target CPP value for favorable outcomes was between 60 mm Hg and 70 mm Hg (8). Elevated ICP could lead to reduction of CPP which might cause a poor prognosis. And elevated ICP could decrease CPP to the point where cerebral blood flow (CBF) might fall to the level that induced ischemia and secondary brain injury. Therefore, not only reduction of ICP but also elevation of CPP in hyperosmolar agent treatment were very important. Our results showed that both HTS and mannitol could increase CPP from the pretreatment level, moreover HTS did it better. However, the I^2 of pooled results was 88%, which means there was an extreme heterogeneity. Following a sensitive analysis, study of Jagannatha, A.T (2) who had the distinct results from others was excluded, but pooled results of other studies showed I^2 was still over 75%. And the pooled result is similar to the former. A reason of heterogeneity might be that difference of CPP between pretreatment and posttreatment level in present processed data was continuous variables with abnormal distribution. And diverse sample sizes might be another reason. Therefore, although pooled results indicated that HTS performed a better effect in increasing CPP, the heterogeneity should be considered.

Except for effect of ICP reduction, option of osmotic therapy should be made based on safety. Mainly

reported adverse events of mannitol treatment included electrolyte disturbances, hypovolemia, hypotension and acute kidney injury. For HTS, there were also several common adverse events included volume overload, severe hypernatremia (>160 mEq/L), acute kidney injury, and the osmotic demyelination syndrome (26). In present review, some eligible physiological indicators like MAP, serum sodium, serum osmolarity, HCT and HR were processed for meta-analyses. As our results indicated, there was no difference in change of MAP between manitol and HTS groups, and effect of elevation of serum sodium and serum osmolarity was better in HTS than in mannitol. Nevertheless, statistic results showed the heterogeneities were extreme (MAP, I^2 = 90%; serum sodium, I^2 = 96%; serum osmolarity, I^2 = 92%). Moreover, changes of HCT and HR had no difference in mannitol and HTS groups. And statistic results show a credible pooled results with no heterogeneity (HCT, I^2 = 15%; HR, I^2 = 13%). Higher serum sodium and serum osmolarity would give a larger osmotic gradient in HTS group than in mannitol group and this might give an interpretation that a better efficacy in reduction of ICP in HTS treatment.

A relationship between hypernatremia and increasing mortality had been described in a general hospitalized patients in a medical intensive care unit (27). And in present included trails, the most common cause of hypernatremia might be iatrogenic, induced by HTS. In a study of HTS therapy in neurocritically ill patients, authors thought the reason of the association between hypernatremia and mortality remained unclear, and an applicable upper threshold for hypernatremia had yet to be determined (28). They also thought that hypernatremia as a reflection of treatment with osmotic agents could be a marker of more severe underlying cerebral injury. Therefore, if an appropriate threshold for serum sodium and osmolarity are made, high level of serum sodium or osmolarity should not be reasons that prevent the application of HTS. Seemingly, patients with hyponatremia should receive HTS treatment. However, rapid change in serum sodium had been considered as a causative factor for central pontine myelinolysis, especially in patients with chronic hyponatremia. Therefore, it should be careful when using HTS in patients with hyponatremia. On the other hand, hyponatremia and hyperkalemia were also the most commonly reported electrolyte abnormalities in mannitol therapy. However, in present meta-analysis of serum sodium, all seven eligible trials did not report any adverse effect about hyponatremia. And for hyperkalemia, there were insufficient data to undergo a meta-analysis. Otherwise, mannitol seemed to have a higher likehood of acute renal insufficiency than HTS. However, in included studies, only one study reported detailed data on blood urea nitrogen, whose results demonstrated no significant difference between HTS and mannitol (6). As a subgroup analysis, there was no sufficient studies. If a further research would be performed, it needs another analysis which renew a specialized subject, so that more eligible trails might be included.

Except for increasing ICP and CPP, lots of studies indicated that mannitol and HTS had other favorable and adverse characteristics which might determine their utilities. As a classical osmotic agent, there was concern about mannitol because of the diuretic effect, which limited its application in patients with systematic hypotension. Moreover, a study indicated that mannitol could increase CBF by inducing blood dilution to decrease viscosity and causing cerebral vasoconstriction (29). Some researchers considered that mannitol had a favorable safety profile although it could cause electrolyte abnormality and renal impairment (30). Different from mannitol, HTS solutions might be preferred in situations requiring rapid cardiovascular resuscitation of associated hemorrhagic shock and arterial hypotension, given the volume expansion and lack of a diuretic effect (31). It was also indicated that compared with mannitol there was no pressure rebound in HTS treatment (32). And HTS could be combined with agents such as dextran or hydroxyethyl starch, which could prolong the circulatory effect of hypertonicity (33). Moreover a research demonstrated that not only reduction of ICP and elevation of CPP, but also improvement of brain tissue oxygen tension (PbtO2) were reported in HTS treatment (34). In addition, several studies indicated that HTS was more effective than mannitol in treatment of refractory intracranial hypertension (34-36). Generally speaking, although a promising trend of HTS treatment in patient with elevated ICP is emerging, precise medicine based on characteristics of mannitol and HTS in different patients would be preferred.

In this study, it was not reported pooled neurological outcomes or mortality. Because diseases in ten trials were not consistent and there was no preferable comparability. And two previous meta-analyses reported the pooled results of neurological outcomes and mortality in patients with TBI (22, 24). Both of them

demonstrated that there was no significant difference between HTS or mannitol therapies for the outcomes of neurological function and mortality. In consideration of lacking new interested data of neurological outcome and mortality, we did not report this repetitive work in this article.

Nevertheless, our study have several limitations. First, this analysis has limited number of eligible studies which likely suffers from a small study effect and low number of events, because of several strict inclusions. And several trails which preferred HTS treatment, are excluded because of lacking exact ICP values. In these trails, number of ICP treatment failure or success was used as primary outcomes. However, this definition of ICP treatment in different trails were ambiguous and inconsistent. Therefore, for reducing heterogeneity, we selected eligible trails which could offer exact quantitative value of ICP. Second, in all included trails, there were several different concentrations of HTS. Moreover there were inconsistent conclusions about whether different concentrations of HTS might have different effects in reduction of ICP or not (37-39). Consequently, the optimal HTS concentration is still not unsettled. And the contradictory conclusions and limitations of traditional meta-analysis suggests that the direct and indirect comparison principle of network meta-analysis may be the most appropriate method to explore the best hypertonic agent for treatment of patients with elevated ICP. In addition, in data processing part, median and range values or IQR values in some included studies were transformed into mean and SD values by certain transformation rules. Theoretically speaking, this transformation is reasonable, however, it might bring some confounders and generate biases and errors. For making up it, sensitivity analysis was performed. Fortunately, results were stable and credible. All of the above may lead to bias to our results.

Conclusions

Our study indicated HTS had a better efficiency in reduction of elevated ICP than mannitol in earlier stage. Based on the current level of evidence related to control of ICP and effect in other physiological indicators, HTS could be recommended as a first-line agent for managing patients with elevated ICP. Nevertheless, more RCTs with high quality are needed to consolidate this recommendation.

Competing interests

There are no competing interests to declare.

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Table 1. Base characteristics of included studies.

Author and publication year	**Region**	**Study design**	**Type of diseases**	**Number of patients or episodes**	**Comparators**	**Comparators**	**Interested change of items in outcome**
Xuecai Huang. 2020	China	RCT, crossover	TBI	n=83; episodes=437	Mannitol 20% mannitol; episodes=221; age: NA; female/male: NA; initial GCS: NA;	HTS 10% HTS; episodes=236; age: NA; female/male: NA; initial GCS: NA;	ICP, CPP, MAP, serum sodium, serum osmolarity, CVP
Patil, H. 2019	India	RCT	TBI	n=80; no episode	20%mannitol; n=40; episodes=NA; age: NA; female/male: NA; initial GCS: NA;	3.0%HTS; n=40; episodes=NA; age: NA; female/male: NA; initial GCS: NA;	ICP, CPP, HR, MAP, HCT, serum sodium, serum osmolarity
Jagannatha, A. T. 2016	India	RCT	TBI	n=38; episodes=488	20%mannitol; n=20; episodes=301; age: 31±13[a]; female/male: 2:18; initial GCS: 5(3-7)[b];	3.0%HTS; n=18; episodes=187; age: 27±8[a]; female/male: 2:16; initial GCS: 4(4-5)[b];	ICP, HR, MAP, serum sodium, serum osmolarity, mortality
HUANG Xue. 2015	China	RCT, crossover	SAH	n=25; episodes=196	20%mannitol; n=95; age: NA; female/male: NA; initial GCS: NA;	3.0%HTS; n=101; age: NA; female/male: NA; initial GCS: NA;	ICP, CPP, MAP, serum sodium, serum osmolarity, VP
Cottenceau, V. 2011	France	RCT	TBI	n=47 no episode	20%mannitol; n=25; age: 36.1±16.8 [a]; female/male: NA; initial GCS: 7(5-8)[c];	7.5%HTS; n=22; age: 42.7±19.9 [a]; female/male: NA; initial GCS: 5(4-7)[c];	ICP, CPP, MAP, HCT, serum sodium, CBF, BUN

Author and publication year	Region	Study design	Type of diseases	Number of patients or episodes	Comparators	Comparators	Interested change of items in outcome
Sakellaridis, N. 2011	Greece	RCT, crossover	TBI	n=29; episodes=199	20%mannitol; episodes=82; age: NA; female/male: NA; initial GCS: NA	15%HTS; episodes=82; age: NA; female/male: NA; initial GCS: NA;	ICP
Ichai, C. 2008	France	Prospective open randomized study	TBI	n=21; episodes=43	20%mannitol; episodes=18; age: NA; female/male: NA; initial GCS: NA;	half-molar sodium lactate; episodes=25; age: NA; female/male: NA; initial GCS: NA;	ICP, CPP
Francony, G. 2008	France	Parallel RCT	TBI, n=17; Stroke, n=3;	n=20; no episode	20%mannitol; n=10; age: 43±11 [a]; female/male: 3/7; initial GCS: 8±2 [a];	7.45%HTS; n=10; age: 37±16 [a]; female/male: 1/9; initial GCS: 7±2 [a];	ICP, serum sodium
Harutjunyan, L. 2005	Germany	RCT	cerebral trauma, spontaneous intracerebral bleeding, SAH	n=32; no episode	15%mannitol; n=15; age: 47±16 [a]; female/male: 7/8; initial GCS: 5.8±1.4 [a];	7.2%NaCl/HES 200/0.5; n=17; age: 47±16 [a]; female/male: 8/9; initial GCS: 6±1.3 [a];	ICP, CPP, HR, MAP, HCT, serum osmolarity
Battison, C. 2005	UK	RCT, crossover	TBI, SAH	n=9; episodes=36	20%mannitol; n=18; age: NA; female/male: NA; initial GCS: NA;	7.5% saline and 6% dextran-70 solution; n=18; age: NA; female/male: NA; initial GCS: NA;	ICP, CPP, MAP, serum sodium, serum osmolarity

a mean ± standard deviation. b median (interquartile range). c median (lower and upper 95% confidence limit of median).

Abbreviations: BUN, blood urea nitrogen; CPP, cerebral perfusion pressure; CVP, central venous pressure; HR, heart rate; ICP, intracranial pressure; MAP, mean arterial pressure; RCT, randomized controlled trails; SAH, subarachnoid hemorrhage; TBI, traumatic brain injury; VP, venous pressure.

Table 2 . Summaries of previous systematic review and meta-analysis.

First Author and Publication date	Design of included studies	Num
Jiajie Gu, 2018	RCT	n=12
Elyse Berger-Pelleiter, 2016	RCT	n=11
Sarah Burgess, 2016	RCT	n=7
Min Li, 2015	RCT; 2-arm prospective studies	n=7
A C Rickard, 2013	RCT	n=6
Martin M. Mortazavi, 2012	RCT; nonrandomized prospective observational trials; retrospective trials	n=36
Hooman Kamel, 2011	RCT	n=5

Abbreviations: CI: confidence interval; MD: mean difference; WMD: weighted mean difference

Figure 1. Flow diagram of study selection.

Figure 2. Risk of bias summary.

Figure 3. Forest plot of general meta-analysis of ICP reduction from pretreatment to first reported records after treatment, comparing mannitol and HTS.

Figure 4. Forest plot of reduction of ICP at different time points, comparing mannitol and HTS.

Figure 5. Forest plot of eligible secondary outcomes (CPP, MAP, Serum Sodium, Serum Osmolarity, HCT, HR), comparing mannitol and HTS.

Figure 6. Assessment of publication bias by a contour-enhance funnel plot.

Supplementary material 1. Data of contour-enhance funnel plot

Supplementary material 2. Egger's test

Supplementary material 3. AMSTAR 2 of previous systematic reviews

Y: yes; N: no; PY: Partial Yes.

Red-labled means critical domains of AMSTAR 2.