A Systematic Review of Treatment Outcomes Following Hyperosmolar Solutions for the Treatment of Brain Edema in Patients with Intracerebral Hemorrhage

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บทคัดย่อ : การทบทวนวรรณกรรมอย่างเป็นระบบในการประเมินผลการรักษาจากการให้สารละลายชนิด hyperosmolar เพื่อรักษาภาวะสมองบวมในผู้ป่วยที่มีเลือดออกในสมอง

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ภูมิหลัง: ภาวะเลือดออกในสมองถือเป็นภาวะฉุกเฉินทางการแพทย์ ซึ่งการรักษาด้วยการผ่าตัดเป็นการรักษาที่มีประสิทธิภาพสูงและหากร่วมกับการรักษาทางยาที่เหมาะสม ย่อมเสริมให้การรักษาได้ผลดียิ่งขึ้น **วัตถุประสงค์:** ทบทวนวรรณกรรมอย่างเป็นระบบเพื่อศึกษาการใช้สารละลาย hyperosmolar ในการรักษาภาวะสมองบวมในผู้ป่วยที่มีเลือดออกในสมอง **วิธีการ:** ทบทวนวรรณกรรมตามแนวปฏิบัติมาตรฐาน โดยสืบค้นรายงานวิจัยที่ตีพิมพ์เป็นภาษาอังกฤษจากฐานข้อมูล Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE ผ่าน Pubmed และ Science direct เพื่อคัดเลือกรายงานวิจัยที่มีผลลัพธ์หลักคือ อัตราการตาย ผลลัพธ์ทางคลินิก และคุณภาพชีวิต รวมถึงผลลัพท์รองคือ ความดันในกะโหลกศีรษะ Glasgow coma scale (GCS) จำนวนวันนอนในหอผู้ป่วยวิกฤติ และผลไม่พึงประสงค์จากการรักษาด้วยสารน้ำ hyperosmolar **ผล:** พบว่ามีรายงานวิจัยเข้าเงื่อนไขในการทบทวนวรรณกรรมจำนวน 5 รายงาน จำนวนผู้ป่วยรวมทั้งหมด 225 ราย โดยสารน้ำ hyperosmolar ที่ใช้รักษาคือ mannitol และ hypertonic saline แต่เนื่องจากข้อกำหนดในรายงานวิจัยแต่ละรายงานแตกต่างกัน รวมถึงสารน้ำ hyperosmolar ที่ใช้ก็แตกต่างกันด้วย จากการวิเคราะห์พบว่าไม่ว่าจะใช้ mannitol หรือ hypertonicsaline ในการรักษาภาวะสมองบวมในผู้ป่วยที่มีเลือดออกในสมอง ผลลัพธ์ด้านอัตราการตาย คุณภาพชีวิต ความดันในกะโหลกศีรษะ Glasgow coma scale (GCS) จำนวนวันนอนในหอผู้ป่วยวิกฤติ และผลไม่พึงประสงค์จากการรักษาด้วยสารน้ำ hyperosmolar ไม่แตกต่างกันอย่างมีนัยสำคัญ ส่วนผลลัพธ์ทางคลินิก ไม่พบรายงานวิจัยใดรายงานผลในเรื่องนี้ **สรุป:** จากข้อมูลหลักฐานในปัจจุบัน ยังไม่สามารถสรุปได้ว่าสารน้ำ hyperosmolar ชนิดใดสามารถลดอัตราการตาย รวมถึงเพิ่มคุณภาพชีวิต ลดความดันในกะโหลกศีรษะ GCS และลดจำนวนวันนอนในหอผู้ป่วยวิกฤติได้ดีที่สุด

คำสำคัญ: ภาวะเลือดออกในสมอง การดูแลผู้ป่วยวิกฤติ ภาวะสมองบวม สารน้ำ ความดันในกะโหลกศีรษะ

Abstract:

Background: The treatment of intracerebral hemorrhage (ICH) is a medical emergency. Surgery has been found to be an effective form of medical treatment. Appropriate medical treatments including hyperosmolar solutions are essential for satisfactory outcomes. **Objective:** This systematic review was conducted to review state-of-the-art hyperosmolar solutions for the treatment of brain edema in patients with ICH. Methods: A systematic review was performed in accordance with established standards for systematic reviews following meta-analyses guidelines. Trials were identified by electronic searches using Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE via Pubmed and Science direct. The primary outcomes measured focused on mortality rate, clinical outcomes and quality of life. Secondary outcomes included intracranial pressure (ICP), Glasgow coma scale (GCS), length of stay in an intensive care unit and adverse effects. Results: Five studies comprising 225 patients were included in the review. Hyperosmolar solutions found in the included studies were hypertonic saline

and mannitol. Their protocols were various, especially the formulation and dose of the solutions. No statistically significant differences were identified in terms of mortality rate, quality of life, ICP, GCS, length of stay in an intensive care unit or adverse effects between mannitol groups and hypertonic saline solution group. No study reported clinical outcomes. **Conclusions:** Current evidence indicates that the effects of hyperosmolar solutions including mannitol and hypertonic saline on mortality rate, quality of life, ICP, GCS and length of stay in an intensive care unit remain undefined.

Keywords: Intracerebral hemorrhages, Critical care, Brain edema, Mannitol, Hypertonic saline

Introduction

The incidence of intracerebral hemorrhage (ICH) is 24.6 per 100,000 adults[1]. This is regarded as one of major causes affecting the global disability and mortality rates. The prevalence is increased in Asian males who have risk factors including hypertension, increased age and high alcohol consumption. Etiology of ICH is various such as hypertension, amyloid angiopathy, brain tumor, traumatic brain injury, underlying structural vascular, coagulopathy, anticoagulation and other medication such as systemic thrombolysis of noncerebral thrombosis[2-4]. With intracranial hypertension as the prognostic factor, this could lead to poor outcomes because of reduced cerebral blood flow (CBF). In severe cases, brain herniation may occur, which can lead to death[5]. Treatment of ICH is a medical emergency in which the majority of patients experience deterioration within a few hours[6]. In addition to prompt diagnostic evaluation and appropriate medical care to increase the survival rate, appropriate anesthetics and critical care are necessary factors affecting treatment outcomes when surgical care is indicated. Therefore, there are many studies and innovation aiming to provide the best-practice[7]. Medical care, ventilation, and monitoring in the treatment of ICH are important, as the appropriate selection of intravenous solutions[8]. In ICH patients, the use of hyperosmolar solutions aims to control cerebral perfusion levels as well as prevent the loss of intravascular volume without increased cerebral edema[9]. One of the properties of hyperosmolar solutions is to reduce brain volume via decreasing intracellular fluid and extracellular fluid compartment[10.] Therefore, they are commonlyused to treat intracranial hypertension including for patients with ICH[11].

In addition to mannitol and hypertonic saline which are commonly used to reduce brain edema due to ICH[7], there are other agents such as glycerol[12] and urea[13]. Though they can effectively reduce intracranial pressure (ICP), they cause different adverse effects. For example, mannitol may cause hypotension, congestive heart failure and electrolyte imbalance[14]. Meanwhile, hypernatremia, injection site infection and severe adverse effects (renal failure and pulmonary embolism) were found when using hypertonic saline[15]. These limit the utilization of hyperosmolar solutions. In order to provide the best treatment for patients, there are many studies comparing the effectiveness of different types of solutions. However, most studies and reviews have compared two types of solutions and recruited patients with stroke[16] or traumatic brain injury (TBI)[17]. Hence, the effectiveness of hyperosmolar solutions to treat brain edema in patients with stroke or TBI remains inconclusive. This may be because these reviews and trials included patients as a heterogeneous group, in which the patients may have different details of pathology such as stroke classified into ischemic stroke and hemorrhagic stroke. Patients with TBI could have a cerebral contusion and intracranial hemorrhage, including ICH.

On the other hand, surgical treatment is found to be effective only in patients with intracranial hemorrhage including epidural hematoma[18], subdural hematoma[19] and subarachnoid hemorrhage[20], but failed to show clinical outcome benefit compared with conservative medical treatment in patients with ICH as reported by analytical studies, RCT and prospective studies[21-23]. Therefore, appropriate medical treatments including hyperosmolar solutions are essential for satisfactory outcomes in patients with ICH. This aspect differentiates patients with ICH from others. Thus, this systematic review was conducted to review the state-of the-art hyperosmolar solutions for the treatment of brain edema in patients with ICH, including different types of hyperosmolar solutions and their effectiveness in terms of mortality, functional outcomes, length of stay in an intensive care unit and other monitoring outcomes.

Material and Methods

Inclusion criteria: *Types of studies:* A randomized controlled trial (RCT) comparing the treatment outcome of hyperosmolar solution for treatment of brain edema in patients with ICH was suitable for inclusion since it is considered the gold-standard in clinical research[24]. *Types of participants:* A trial was included if it studied only adult participants(> 18 years of age) of either gender who had been diagnosed with ICH (spontaneous and traumatic ICH). Participants having a diagnosis of ICH as a result of coagulopathies, arteriovenousmalformation and tumors were excluded. *Types of interventions:* The intervention could be hyperosmolar solutions including mannitol, hypertonic saline, glycerol and urea[25]. Comparisons between different hyperosmolar solutions or hyperosmolar solutions versus control were included. Types of outcome measures: Primary outcomes: 1. Longest follow-up mortality[26] 2. 6-month clinical outcome (Glasgow outcome scale)[27] 3. Quality of life assessment[28] Secondary outcomes: 1. Evolution of intracranial pressure (ICP)[29] 2. Glasgow coma scale (GCS)[30] 3. Length of stay in an intensive care unit[31] 4. Adverse effects[14, 15]

Search methods for the identification of studies: Trials were identified by electronic search using the Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE via Pubmed and Science direct which have many reliable medical literature. Publication date since 2000/01/01 was applied for make sure that the most recent data which have current medical knowlegde was selected. MESH terms and keywords were searched by title, keywords and abstracts in combinations using Boolean operators: “AND”, “OR”, “NOT” as appropriate with restrictions (Publication date from 2000/01/01 to 2018/11/20; Humans; English; Adult), as follows: *MESH terms:* Terms included hypertonic solutions, mannitol, glycerol, urea, intracranial hemorrhages, stroke, intracranial pressure, brain edema *Keywords:* Stroke, intracranial, intracerebral, hemorrhage, hemorrhages, CVA, cerebrovascular accident, saline, hyperosmolar, hypertonic saline, saline solution, mannitol, sorbitol, sodium, bicarbonate, glycerol, glycerin, glycerine, trihydroxypropane, urea, basodexan, carbamide, carmol, oedema, edema, swell, pressure, hypersensitive, brain.

Data collection and analysis: *Selection of study:* Using the results of the above searches, duplications were removed. All titles and abstracts were screened for relevance and eligibility (Rayakorn Moonla). Full papers were obtained and assessed for inclusion criteria as mentioned above (Rayakorn Moonla). A list of all eligible papers was compiled[32-3] 6. Data extraction and management: Two reviewauthors independently extracted the data and assessed paper quality using a customized data extraction form (Rayakorn Moonla, Pornsuree Kuvijitsuwan). *Assessment of risk of bias in included studies:* Two review authors (Rayakorn Moonla, Phuping Akavipat) independently assessed the risk of bias and resolved disagreements through a third review author (Pornsuree Kuvijitsuwan). The assessment was performed as suggested in the Cochrane Handbook for Systematic Reviews of Interventions (Higgin, 2011), judging the risk of bias for included studies on the basis of the following domains: 1. Random sequence generation 2. Allocation concealment 3. Blinding of participants, personnel and outcome assessor 4. Incomplete outcome data 5. Selective outcome reporting. Papers were considered to have a low risk of bias if all domains were assessed as adequate and considered to have a high risk of bias if one or more domains were assessed as inadequate or unclear based on the data described in the paper. *Measures of treatment effect:* Data analysis was performed, where appropriate, with the use of statistical software, Review Manager 5.3, of The Cochrane Collaboration. Risk ratios (RRs) was used to measured treatment effect for proportions (dichotomous outcome). Continuous data was converted to mean differences (MDs) using the inverse variance method, and an overall MD was calculated. A fixed-effect model was used when no evidence of significant heterogeneity was found between studies, while a random-effects or fixed-effect model was used when heterogeneity was likely (DerSimonian, 1986). As an estimate of statistical significance of the difference between experimental and control interventions, RRs and MDs between groups was calculated, as well as 95% confidence intervals (CIs). A statistically significant difference between intervention and control groups was assumed if the 95% CI did not include the value of no differential effect. *Unit of analysis issues:* Only RCTs with a parallel-group design were included. *Assessment of heterogeneity:* If important clinical heterogeneity on the examination of the included trials was suspected, meta-analysis was not performed. The Q statisticwas used to test statistical heterogeneity between trials and a P value ≤ 0.05 was considered as indicating significant heterogeneity. The I^2 statistic was used to assess the magnitude of heterogeneity (Higgins, 2002). I^2 > 50% was considered to indicate that a meta-analysis was not appropriate and a random-effects model analysis was used if I^2 was between 30% and 50%. *Data synthesis:* The included data was quantitatively reviewed and combined by intervention, outcome, and population, using Review Manager 5.3. Data was synthesized in the absence of important clinical or statistical heterogeneity and expressed risk ratios for proportions.

Results

Description of studies: The electronic searches yielded 1192 records. After the removal of duplicates and irrelevant data, five studies were included (Fig. 1).

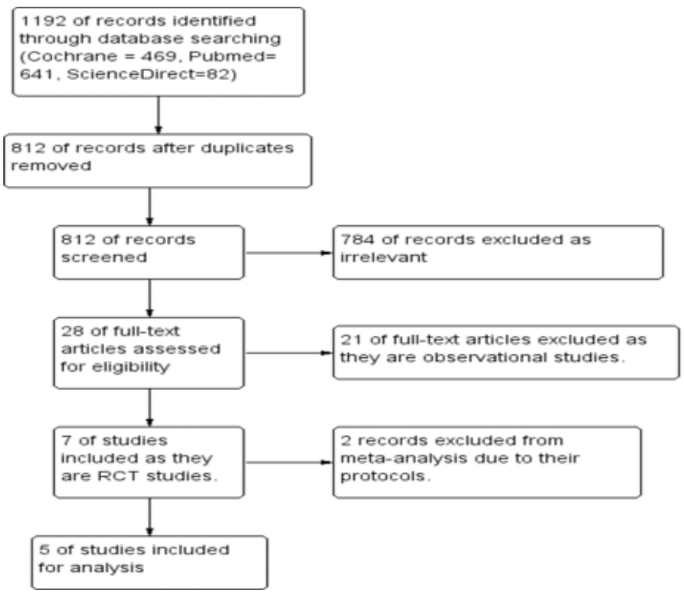

Fig.1 Study flow diagram

Included studies: Five studies wereincluded in the final analysis (Table 1). 225 patients were involved, aged between 21 and 80 years. Hyperosmolar solutions found in included studies were only hypertonic saline and mannitol. Comparisons were made between mannitol and hypertonic saline[32, 33], mannitol and normal saline [34-36]. Their protocols were varied, especially theformulation and dose of the solutions. According to the definition of ICP control or raised ICP, two studies were not mention, two studies used a specific value for start or stop infusion, and one study utilized clinical signs indicating raise ICP. Two of three studies comparing between mannitol and normal saline concluded that low dose mannitol did not improve mortality rate, functional outcome or regional cerebral blood flow, while the remaining studies showed improvement in MRI parameters. The results from the two studies comparing mannitol and hypertonic saline were inconsistent.

Excluded studies: Two studies were excluded. Wang et al.'s study[37] was a multicenter study and their protocol compared mannitol and non-mannitol solutions which were various depending on local protocols. Cruz[38] compared high dose and low dose mannitol which was not compliant to the inclusion criteria for this research.

Risk of bias: The characteristics of included studies used for assessment of the risk of bias are shown in Fig. 2 and Fig. 3. All outcomes stated in the study protocol were reported in five included studies. However, only one of the five included studies(Francony[32]) did not describe the blinding process. Kalita[36] was graded as having a high risk of bias in incomplete outcome data due to unsatisfactory radiologic imaging.

Effect of interventions: The research questions were answered as follows: *Primary outcomes:* 1. Longest follow-up mortality: Three studies reported mortality rate. One study compared mannitol and hypertonic saline assessed at the end of stay in an ICU (Harutjunyan[33]), while two studies (Kalita[36], Misra[34]) compared mannitol and normal saline assessed at 1-month follow-up. None reported statistically significant differences in mortality rate between mannitol groups and hypertonic saline/normal saline solution group. The meta-analysis could not be conducted due to the small number of papers reported. 2. Six-month clinical outcome (Glasgow outcome scale): No study reported this outcome. 3. Quality of life assessment: All included studies did not make mention of quality of life, though one study (Misra[34]) reported on functional disability at the end of 3 months as assessed by Barthel index score, which found that there was no statistically significant difference between the mannitol group and normal saline group. *Secondary outcomes:* 1. Control of intracranial pressure (ICP): Two studies continuously monitored ICP. Harutjunyan[33] reported that 7.2% hypertonic saline was more effective than 15% mannitol for the treatment of increased ICP. In contrast, Francony[32] reported that a single equimolar infusion of 20% mannitol was as effective as 7.45% hypertonic saline. The meta-analysis could not be conducted due to the small number of papers

Table 1 Characteristics of included studies

First author, year	Patients (number of patients)	Group	Number of patients	Gender(M/F)	Age (year)	Definition of raised ICP or ICP control	Formulation	Dose	Summary
Harutjunyan et al, 2005	TBI(10) Stroke(7) SAH(9) ICH(4) Other(2)	Mannitol NaCl/HES	15 17	8/7 9/8	47(SD 16) 47(SD 16)	< 15 mmHg (stop infusion)	15%	until ICP < 15 mmHg	7.2% NaCl/HES 200/0.5 is more effective than mannitol 15% in the treatment of increased ICP.
Francony et al, 2008	TBI(17) ICH(2) Stroke (1)	Mannitol Hypertonic saline	10 10	7/3 9/1	43(SD 11) 37(SD 16)	>20 mmHg	20% 7.45%	231 ml 100 ml	A single equimolar infusion of 20% mannitol is as effective as7.45% Hypertonic saline in decreasing ICP in patients with brain injury.
Misra et al, 2007	ICH (43)	Mannitol Normal saline	12 12	11/1 8/4	57.8 (SD 7.2)	Clinical signs: GCS score, pupillary asymmetry, CNS score, extensor posturing and hyperventilation	20% 0.9%	1.5 gm/kg	In ICH patients, mannitol results in transient clinical improvement without significant changes in midline shift and, SSS-PMJ distance on MRI.
Misra et al, 2005	ICH(128)	Mannitol Normal saline	65 63	47/18 49/14	56.0 (range 35-80)	Not specified	20% 0.9%	3,500 ml in 7 days	Low dose mannitol does not seem to be beneficial in patients with ICH.
Kalita et al, 2004	ICH(21)	Mannitol Normal saline	12 9	11/1 6/3	55.6 (range 46-71)	Not specified	20% 0.9%	0.33 g/kg	Mannitol does not seem to significantly change the regional cerebral blood flow in ICH patients as evaluated by SPECT study.

reported and only one paper showed standard deviation. 2. Glasgow coma scale (GCS): Three studies (Harutjunyan[33], Francony[32], Misra[34]) used GCS as inclusion criteria, but it was not used as a measured outcome. Two other studies reported the GCS (Misra[35]and Kalita[36]) without any statistically significant difference in either mannitol or normal saline group after infusion. 3. Length of stay in an intensive care unit: Only Harutjunyan[33] reported no statistically significant difference for days in ICU for 15% mannitol group and 7.2% hypertonic saline group. 4. Adverse effects: Only Misra[36] reported that a patient developed hyponatremia (not severe) following mannitol therapy and was treated by oral sodium chloride supplementation.

Discussion

This review analyzed randomized control trials investigating the use of hyperosmolar solutions in patients with ICH. The objective was to review state-of the-art hyperosmolar solutions for the treatment of brain edema in patients with ICH, including the different types of hyperosmolar solutions and their effectiveness in term of mortality, functional outcomes, and other monitoring outcomes such as ICP, GCS, length of stay in an intensive care units and adverse effects. Participants: Studies consisting of clearly stated ICH participants were included regardless of focused groups: TBI, stroke or neurosurgery. This ensured that all studies carried out in patients with ICH were

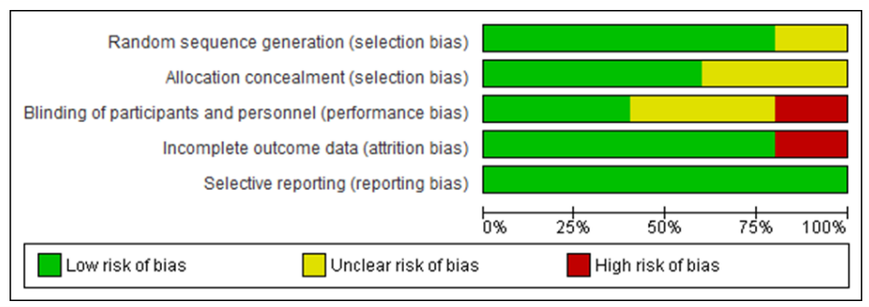

Fig. 2 Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies

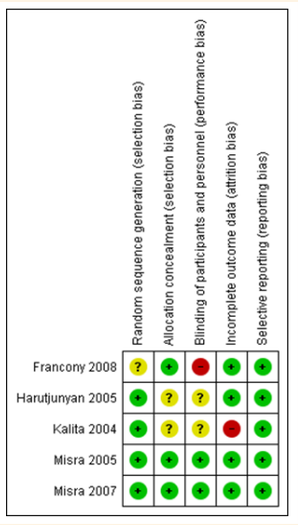

Fig. 3 Risk of bias summary: review authors' judgements about each risk of bias item for each included study.

included and/or reviewed. However, the analysis of the studies comprising patients with and without ICH (Harutjunyan[33], Francony[32]) could be challenging as the outcomes may not be specific to a particular ICH group. Although all studies on hyperosmolar solutions with potential implications for patients with ICH were included, the number of included studies was small. Thus, meta-analysis could not be carried out. A few of the included studies emphasized the need for further research on this focused group. *Hyperosmolar solutions:* There were three different solutions found in five studies included in this review: hypertonic saline, mannitol and normal saline. Normal saline was used as a control in experiments except for two studies did not used control solution (Harutjunyan[33], Francony[32]). Only hypertonic saline and mannitol hyperosmolar solutions were investigated. Similar to other systematic reviews[16-17,39], Gu[17]reviewed hyperosmolar therapy for the treatment of ICP in TBI. They focused only on hypertonic saline and mannitol, while Bereczki16reviewed mannitol in ischemic stroke and cerebral parenchymal hemorrhage, Prabhakar-[39]reviewed the use of mannitol versus hypertonic saline in brain relaxation in patients undergoing craniotomy. They chose to review mannitol, which is regarded as the gold standard[40]. To avoid the adverse effects of mannitol, hypertonic saline became one of the alternatives. In addition to the aforementioned agents, glycerol[12], urea[13], sorbitol[41] and sodium bicarbonate[42] are also used as hyperosmolar agents. However, they do not appear in our included studies. One of the reasons may be that their benefits have not been proven. Therefore, glycerol, urea, sorbitol and sodium bicarbonate are unlikely to be administrated in recent studies and medical practice. Likewise, other agents may have been investigated before 2000, but the outcomes were not shown to be beneficial. There are only five studies consisting of patients with ICH and the number of recruited patients is relatively small. Therefore, generalizability is limited. Similar to review papers written by Prabhakar[39], Bereczki[16] and Gu[17] their included studies comprised 6, 1 and 12 RCTs with 300-527 recruited patients. All included studies did not statistically calculate sample size. This maybe because, in critically ill patients, ethical considerations exist and informed consent can be difficult to obtain. The protocols described in the included studies are various. This is affected by local guidelines. Without published evidence-based practice, different sites can administrate a variety of standards for care, dose, concentration, infusion techniques, and recorded outcomes of hyperosmolar solutions. This heterogeneity makes

the meta-analysis from different sites impossible. Therefore this review can only describe the overall outcomes. For the treatment of increased ICP, Harutjunyan[33] and Francony[32] found that 20% mannitol was as effective as 7.45% hypertonic saline for decreasing ICP and 7.2% hypertonic saline was more effective than 15% mannitol in the treatment of increased ICP. However, other given care in the treatment of ICP elevation can be different for other sites and studies. In order to investigate the most effective dose, different doses should be compared with other controlled variables. We found only one study comparing different doses of mannitol[38]. A high dose seemed to be better for improvement of long-term clinical outcomes. Our study focused on the primary outcomes reflecting heath management and found no statistically significant differences in terms of mortality rate, quality of life, ICP, GCS, length of stay in an intensive care unit and any adverse effects between mannitol groups and hypertonic saline/normal saline solution groups. None of the study reports clinical outcome. A meta-analysis of randomized controlled trials by Gu[17] compared the use of hypertonic saline versus mannitol for treating elevated intracranial pressure in TBI. The results did not offer a specific recommendation for the selection of hypertonic saline or mannitol as the first-line for patients with elevated ICP caused by TBI. A systematic review of mannitol therapy for acute stroke by Bereczki[16] reported that no evidence supported the routine use of mannitol for patients with acute stroke. A systematic review by Prabhakar[39] compared the use of mannitol versus hypertonic saline for brain relaxation in craniotomy, which concluded that there were no benefits of any fluid over one another for use during the intraoperative period. Their result found no benefit of hypertonic saline or mannitol use in terms of mortality rate, clinical outcomes and adverse events as in our review. The size of a hematoma and the severity of patients could be factors affecting outcomes. Many studies did not report on hematoma size. Only Misra[34] showed a CT scan reporting hematoma size in small, medium and large groups. Therefore, this should be considered for medical care and future research. Another factor is the severity of patients. This may vary across different studies, making comparisons difficult. Limitations: There are a few limitations in this review. Firstly, the main limitation of this review was an inability to conduct meta-analysis because of the heterogeneity of protocols, different outcomes measured and the different presentations of the same outcomes. For example, decreased ICP were reported in three studies but two of them reported mean without standard deviation. One of the included studies presented clinical signs indicating increased ICP. Secondly, a small group of studies and populations results in difficult generalizability. Three in five studies conducted by the same researchers may potentially have risk of bias. Thirdly, all published trials were limited to English language. Thus a number of unpublished studies or studies in other languages may have been omitted. Finally, many studies focusing on patients with TBI, stroke or neuro surgery did not state whether their participants presented with ICH. These studies were excluded base on the inclusion criteria. Therefore, some useful data may have been omitted. Recommendations for future research: Experiments comparing different types of hyperosmolar solutions including mannitol and hypertonic saline focusing on patients with ICH should be conducted with strictly controlled affecting factors to find the most effective agent to reduce brain edema. The formation and dose of hyperosmolar solutions should also be considered. The sample size should be calculated and reported prior to data collection to empower the results. ICP monitoring is recommended[43].

Conclusion

The effect of a hyperosmolar solution including mannitol and hypertonic saline on mortality rate, quality of life, ICP, GCS and length of stay in an intensive care unit remains undefined based on the evidence found in this review. Although there is a RCT, prospective study focusing on this group of patients, the number of studies and recruited participants are relatively small resulting in inconclusive use of hyperosmolar solutions. The formulations and doses are even more undefined.

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