EFFICACY OF 20% MANNITOL VERSUS 3% HYPERTONIC SALINE IN DECREASING INTRACRANIAL PRESSURE IN THE PEDIATRIC AGE GROUP: A SYSTEMATIC REVIEW

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ABSTRACT

Objective: This systematic review aimed to assess the available data on the efficacy of 20% mannitol and 3% hypertonic saline in achieving the primary outcome of decreasing intracranial hypertension in the pediatric age group. Secondary outcomes such as GCS scores, hospital stay, discharge and disabilities were also considered.

Method: Search done through PubMed/MEDLINE, Cochrane Central Registry of Clinical Trials (CENTRAL) and EMBASE yielded 280 studies.

Results: Of 280 studies reviewed, 7 studies with a total of 1,892 pediatric patients met the eligibility criteria: 3 RCTs and 4 retrospective studies. From these, two randomized controlled studies showed statistically significant evidence that 3% hypertonic saline was superior to 20% mannitol in reducing increased intracranial pressure (ICP) while two other studies had results that were insufficient to establish statistical significance. Relative risk of mortality was comparable in both groups. There was a low risk of bias for randomized trials and fair to high quality retrospective studies. Heterogeneity was present as number of outcome measures varied among studies.

Conclusion: This review showed that while both agents effectively decreased intracranial pressure, 3% hypertonic saline showed better results compared with 20% mannitol. Due to the limited number and heterogeneity of studies, a pooled analysis of the effects in ICP could not be done. Larger prospective controlled studies using 20% mannitol and 3% hypertonic saline in the treatment of increased ICP in the pediatric age group are needed to render valid affirmations.

Keywords: Mannitol, Hypertonic Saline, Intracranial Pressure

INTRODUCTION

Increased intracranial pressure (ICP) is one of the most common neurologic emergencies. It is defined as sustained ICP of more than 20mmHg [1] Incidence of increased ICP depends on the primary pathology. Different etiologies such as central nervous system infections, traumatic brain injury, hemorrhage, vascular compromise, neoplasms, hydrocephalus, metabolic and others, lead to expansion of the different compartments within the cranium. This then results to an interplay of pressure, compliance, autoregulation, and overall cerebral perfusion. Persistence of hypertension and compromise of cerebral blood flow leads to complications such as herniation syndromes and focal or global ischemia. [2]

In 2019, a consensus in the stepwise management of intracranial hypertension specifically among patients suffering from severe traumatic brain injury was proposed by Kochanek. In the algorithm, baseline treatment is followed by tiers of treatment. Baseline management are geared towards addressing emergent issues such as maintenance of adequate ventilation, insertion of central line catheters and ICP monitors, initial neuroimaging, analgesia, and sedation, addressing intravascular status, positioning and anti-epileptic drug therapy. First tier of treatment addresses intracranial pressure and cerebral perfusion, primarily by utilizing medical decompressant therapy.[3] Refractory cases are addressed by second tier therapy such as surgical decompression, barbiturate, and hypothermia.

At present, common therapies for medical decompression include osmotic agents such as Mannitol, Hypertonic Saline Solution and Glycerol. Osmotherapy functions by creating an osmotic gradient resulting to decrease in the water content from the interstitium into the intravascular space.[4] A solution of 20% Mannitol, a 6-carbon hexahydric alcohol, has a serum osmolality of 1098mOsm/kg. Since

the early 1900s, its therapeutic effect for decreasing ICP has been observed. [5]

During the recent years, a growing number of studies have been made in assessing the role of hypertonic saline in the control of intracranial hypertension. In 2020, guidelines for the management of cerebral edema were made by a panel constituted by the Neurocritical Care society. While they suggested the use of hypertonic saline over mannitol in traumatic brain injury (TBI) and intracranial hemorrhage, they noted using either mannitol or hypertonic saline for acute ischemic stroke.[6] In the pediatric age group, several studies have reported the use of both mannitol and hypertonic saline in decreasing intracranial pressure medically. However, there are no established guidelines yet on the indication of using one over the other for children.

Intracranial pressure is defined as the pressure within the fixed cranium composed of the brain parenchyma, cerebrospinal fluid, and the intravascular volume. Normal pressure ranges between 5 to 15mmHg [4] Pathologies leading to a change in any of the three components, as stated in the Monroe-Kellie Doctrine, leads to a compensatory alteration in the other compartments. Morbidity and mortality of increased intracranial pressure is associated with the etiology and duration. Persistence and failure of mechanisms later lead to compression of structures, increasing intracranial pressure and subsequent loss of autoregulation and vascular compromise.[1] In children, common etiologies causing increased intracranial pressure include traumatic brain injury, hydrocephalus, intracranial hemorrhage, neoplasms, ischemia, cerebral edema and other metabolic causes.

Hyperosmolar therapy has been used as part of the tiers of treatment in the management of intracranial hypertension. Mannitol is a six-carbon sugar alcohol that functions by the decreasing blood viscosity and increasing

plasma osmolality. This shifts fluid from the extracellular space towards the intravascular compartment resulting to the desired effect of decreasing intracranial pressure.[7] It is available in different concentrations such as 5%, 20% and 25%. The most available and commonly used being the 20 grams in 100mL fluid or the 20% concentration.[8] It is given at a dose of 0.5g/kg to 1g/kg given via rapid infusion. Hypertonic saline has also been utilized as an osmotherapeutic agent. Its use causes increase in the intravascular volume and osmolality which results to shifting of fluids and consequent decrease in intracranial pressure. It is available in different concentrations from 3%, 6%, 12% and 23.4%, with the 3% being the most used. In a study by Sabers et al, their review showed a significant decrease in the intracranial pressure and improved cerebral perfusion pressure with increased concentrations of hypertonic saline.[9] In the same study, hypertonic saline was given via fluid boluses as well as combination of continuous infusion with intermittent boluses. The patients given continuous infusion had better fluid balance when compared to those with rapid boluses.

Primary outcomes measured in the use of these decompressants include improvement of Glasgow coma scale scores, morbidities, mortality, and length of hospital stay. In a randomized control study by Mangat on patients 16 years and older diagnosed with severe TBI, they noted that patients given hypertonic saline had decreased cumulative ICP burden as compared to the 20% mannitol group. However, the mortality rates between the two were not statistically significant.[10] A prospective study by Khanna et al on the use of 3% hypertonic saline via continuous infusion on pediatric patients with severe refractory intracranial hypertension due to traumatic brain injury showed decrease in intracranial pressure and consequent improvement on cerebral perfusion associated with increasing serum sodium and serum osmolality. In the study, continuous infusion

was titrated up over a mean duration of 7.6 days until the desired ICP level of less than 20mmHg was achieved.[11]

In a meta-analysis by Zhang et al, sixty-five reports on the complications of mannitol were assessed. Some of the identified complications included acute renal failure, pulmonary edema, cardiac arrest, bundle branch block, hypertonic hyponatremia, hyperkalemia, hypertension or hypotension as well as subcutaneous infiltration. Hypertonic hyponatremia was noted to be due to the increased solute load and increased urinary sodium loss, while hyperkalemia was linked to changes in bicarbonate concentration and movement of potassium along with water from the extracellular space.[5] A study by Kamel et al (2011), reviewed and analyzed randomized control trials comparing the use of hypertonic saline and mannitol in adult patients with increased intracranial pressure of varying causes such as traumatic brain injury, tumors and intracranial hemorrhage. Upon analyzing five RCTs with a total of 112 patients that met the criteria, their assessment showed greater quantitative ICP reduction with the use of hypertonic saline compared to mannitol [12] with a relative risk of 1.2 (95% CI, 1.05-1.36, $p = 0.007$).

For application in clinical practice, we assessed studies supporting the effectiveness of 20% mannitol compared with 3% hypertonic saline in decreasing intracranial pressure in the pediatric age group. Our general objective was to determine the effectiveness of 20% Mannitol and 3% Hypertonic Saline in the management of children presenting with increased ICP. Our specific objectives were: (1) To review and compare the effective dose for mannitol and hypertonic saline in decreasing ICP. (2) To determine differences in effectiveness of 20% mannitol versus 3% hypertonic saline in achieving the primary outcome of decreasing elevated ICP and achieving ICP levels of <20mmHg in patients with different

pathologies: primary intracranial pathologies and other secondary pathologies. ICP levels are determined using intracranial/ ventricular ICP monitors or utilizing cerebral perfusion and mean arterial pressure. Secondary outcomes such as GCS scores, hospital stay, discharge and disabilities will also be assessed. (3) To determine the common complications related to the use of either 20% mannitol or 3% hypertonic saline seen in the pediatric age group.

MATERIALS AND METHODOLOGY

A systematic review of randomized control trials, retrospective and prospective cohort studies was done. The review included studies consisting of male and female subjects less than 19 years old. Literature search was conducted through PubMed/MEDLINE, the Cochrane Central Registry of Clinical Trials (CENTRAL) and EMBASE. Free text and medical subject heading terms were used to identify studies involving the target population and interventions. Search words included the following: "Mannitol" or "20%Mannitol", "Hypertonic Saline" or "3% Hypertonic Saline", "Increased Intracranial Pressure" and "Pediatrics or Children". Other keywords related to increased intracranial pressure such as "Intracranial hemorrhage, CNS infections, traumatic brain injury, intracranial neoplasms/ tumors, neurosurgical, hydrocephalus" were also assessed. The review included literature with available full text articles written in English from year 1965 to year 2021. It included randomized control trials involving human subjects ages less than 19 years old. It utilized randomized control trials with subjects who exhibited increased intracranial pressure of any cause and were admitted and given 20% mannitol and 3% hypertonic saline. Articles with varying manner of infusion and measurement of ICP were included in the study. Prospective observational studies and retrospective studies were also included. Studies involving patients who were given co-interventions to control ICP but were not directly compared to the interventions

under study were included in this review. References from related review articles and clinical trials were cross checked and included in the review.

Two investigators conducted independent searches to decrease possible risk of bias. After assessing eligibility using the inclusion and exclusion criteria, risk of bias assessment was done. After which, the two independent investigators extracted and collated information using a data form. Primary data included demographic information such as the research design, objectives, the number of subjects. Pertinent data on the different intervention arms, ICP monitoring, pathology causing increased intracranial pressure and the use of mannitol and hypertonic saline were assessed. The dose, manner and timing of delivery were also noted. Primary and secondary outcomes from each study such as decrease in ICP, GCS scores, hospital stay, discharge disability and complications were noted. Evaluation for the quality of studies was done using the Cochrane Collaboration Risk of Bias assessment tool. Parameters included randomization, allocation concealment, sequence generation, completeness of outcome, completeness of follow-up, blinding of outcome assessors, selective outcome reporting and other bias. All studies included for analysis were classified as having low, medium, or high risk of bias. The Newcastle-Ottawa Scale was used for observational studies.

A narrative summary of data was provided when studies have significant differences in methodology. Meta-analysis was performed when at least three studies have similar target patient population, adequate sample size and comparable methodology in the assessment of primary and/or secondary outcomes. The Dersimonian and Laird random-effects model was used to account for heterogeneity among the clinical trials. Higgins' I^2 and Cochran's Q statistic was used to assess heterogeneity of studies. Analysis using fixed effects model

was also performed for comparison. Estimates for mean and SD were estimated when median and interquartile range, range or 95% CI were reported in the studies. Sensitivity analysis was also performed to examine the effects of statistical assumptions. The pooled estimate of the standardized mean difference and 95% confidence interval (CI) were reported for decrease in ICP. Pooled relative risk (RR) with 95% CI were estimated for mortality. Statistical significance was based on p-value ≤0.05. Review Manager (Revman) computer program (Version 5.4.1, Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014) was used in data processing and meta-analysis.

RESULTS

A comprehensive search was done through PubMed/MEDLINE, Cochrane Central Registry of Clinical Trials (CENTRAL) and EMBASE. The initial search of articles was done with the following search items: "mannitol", "hypertonic saline" in relation to "intracranial pressure" and a total of 280 studies was noted. Duplicates between searches, studies not written in English as well as those including non-human subjects were removed. After limiting the search to the studies on the pediatric age group (less than 19 years old), a significant number of articles were excluded since majority of studies were included adult subjects. After further excluding other types of studies as well as articles that did not discuss a comparison between the two interventions, a total of 7 articles were deemed eligible for assessment. (Figure 1).

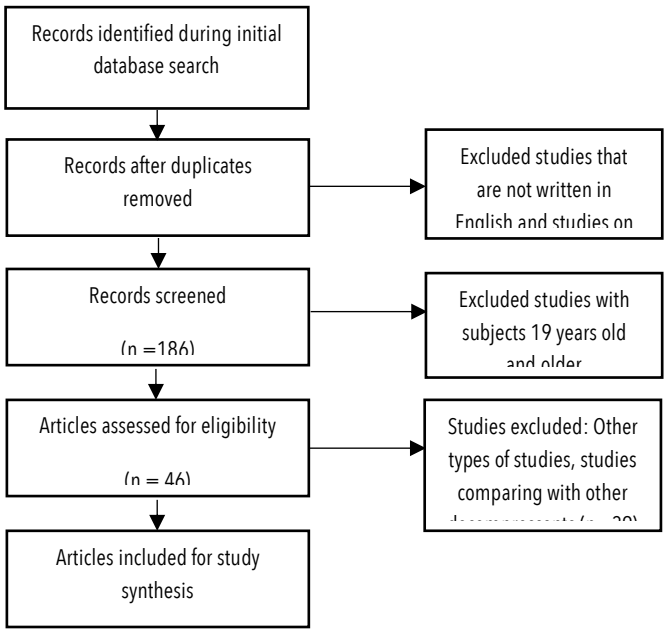

Figure I. Diagram of Study Selection

A prospective randomized control trial done in 2014 comparing the use of 20% Mannitol and 3% Hypertonic Saline among neonates with signs of increased intracranial pressure at the neonatal ICU was not included due to the unavailability of a full text article. A total of seven studies with a total of 1,892 pediatric patients met the eligibility criteria: three RCTs and four retrospective reviews. Study population for the various studies varied from a minimum of 16 subjects to a maximum of 1,632 subjects. The ages of patients ranged from 1 month to <19 years. Characteristics of the studies included in the systematic review are shown in Table I and details of the primary and secondary outcomes are in Table II. Two studies included children presenting with increased intracranial pressure due to traumatic brain injury. The rest of the studies included varying etiologies of increased ICP such as infection (viral and bacterial), hemorrhage, tumors, trauma as well as metabolic causes. Invasive and non-invasive modalities may be done in monitoring increased ICP. Invasive modalities include intraparenchymal catheter and external ventricular drains while some non-invasive measures include transcranial

doppler, optic nerve sheath diameter measurement, tympanic membrane displacement, Visual evoked response, tonometry, pupillometry, neuroimaging with cranial CT or MRI. Currently, the use of an external ventricular drain is considered as the gold standard. In the study, Intracranial monitoring was done in four out of the seven studies. For these studies, an intraparenchymal probe or an intraventricular catheter was used. Other means of monitoring utilized mean arterial pressure calculation and monitoring of various clinical and neuroimaging parameters.

A concentration of 20% Mannitol and 3% Hypertonic Saline was used all the studies assessed. Out of the seven, five studies reported administration of mannitol and hypertonic saline via intravenous boluses. In the study by Rameshkumar et al (2020) [13] an initial bolus of hypertonic saline was given. After which, maintenance doses were given via continuous infusion. Majority of the studies reviewed had dosages within the range of the pediatric dose of 0.25g/kg to 1g/kg for 20% mannitol and 5ml/kg bolus for Hypertonic saline. Three out of seven studies gave equiosmolar doses of mannitol and hypertonic saline. The study by Upadhyay et al [14], utilized a loading dose of 5ml/kg followed by a maintenance dose of 2ml/kg every 6 hours for both mannitol and hypertonic saline. Pre and post infusion ICP values showed significant decrease in the hypertonic saline group specifically during the initial 12 hours of infusion. On the other hand, in the study by Kumar et al [15], equiosmolar doses of mannitol (0.5g/kg or 2.5ml/kg) and hypertonic saline (2.5ml/kg). Mean dose frequency was also specified showing frequency of mannitol delivery at 3.25 doses/day versus hypertonic saline at 4.5 doses/ day. While their study utilized equiosmolar doses and had comparable dose frequency, difference in decrease in ICP was not statistically significant. In the retrospective study by Roumelliotis et at [16],

mannitol dosing (0.6g/kg +/- 0.2) and subsequent osmolality load was higher when compared with hypertonic saline (1.8ml/kg +/- 0.7). For the study, even with higher doses, resultant decrease in ICP was still comparable.

Table 1. Characteristics of studies included in the Systematic Review

Author/ (Year)	Study Design	Age range	Number of patients	Etiologies	ICP monitoring	Formulation /Route		Dose	
						Mannitol	3%HTS	Mannitol	3%HTS
1.Upadhyay et al. (2010)	RCT	2-18 years old	Total N=200 patients Mannitol = 98 3% Hypertonic = 100 Mannitol shifted to 3% = 2	Infection (Meningoencephalitis) Hemorrhagic, Anoxia, Trauma, Space occupying lesion, Infarction	Mean arterial pressure (pre and post drug)	20%/ IV	3% /IV	1g/kg (5ml/kg) bolus then 0.4g/kg (2ml/kg) every 6 hours	Initial (5ml/kg), then 2ml/kg every 6 hours
2.Rameshkumar et al. (2020)	RCT	1-12 years old	Total N= 57 Mannitol =28 3% Hypertonic = 29	Japanese Encephalitis, HSV, Enterovirus, Pneumococcus, Hib, Scrub typhus	Intra-parenchymal catheter (CODMAN, ICP inducer probe), CPP	20%/ IV	3% /IV	0.5g/kg bolus over 20 minutes	10ml/kg loading followed by 0.5-1ml/kg/hr continuous infusion
3. Kumar et al. (2018)	RCT	1-16 years old	Total N=30 Mannitol =16 3% Hypertonic =14	Severe Traumatic Brain Injury	Intraventricular device, Clinical* and Neuroimaging** parameters	20%/ IV	3% /IV	0.5g/kg bolus (1098 mOsm)	2.5ml/kg bolus (1027 mOsm)
4. Vats et al. (1999)	Retrospective Cohort	9 months – 16 years old	Total N=43 Mannitol =18 3% Hypertonic = 25	Closed Head Injury, Intracranial Neoplasm, Fulminant Hepatic Failure, Viral Encephalopathy	Intraparenchymal monitor	20%/ IV	3% /IV	0.5g/kg or 1g/kg bolus	5ml/kg
5. Yildizdas et al. (2005)	Retrospective Study	1y 6mon – 10y 3mon	Total N= 67 Mannitol = 22 3% Hypertonic = 25 Mannitol + 3%HTS = 20	Meningoencephalitis, HIE, Intracranial Hemorrhage, Meningitis, Metabolic Encephalopathy	Clinical* and Neuroimaging** parameters	20%/ IV	3% /IV	0.5g/kg initial then 0.25g/kg bolus	0.5-2ml/kg infusion and 1ml/kg bolus over 15 minutes

6. DeCourcey et al. (2009)	Retrospective Cohort	8y 7mon – 15y 2mon	Total N=1,632 Mannitol = 1,202 3% Hypertonic = 299 Mannitol + 3% HTS = 131	(CEDKA) Cerebral Edema in Diabetic Ketoacidosis; Diabetes with hyperosmolar state, diabetes with coma	Neuroimaging parameters	20%/ IV	3% /IV	Not specified	Not specified
7. Roumeliotis et al. (2016)	Retrospective Study	10-15 years old	Total N=16 Mannitol = 3 3% Hypertonic = 13	Severe Traumatic Brain Injury	Intra-parenchymal catheter or Mean arterial pressure	20%/ IV	3% /IV	0.6g/kg +/- -0.2 bolus	1.8ml+/- 0.7ml; 50% also received continuous infusion 0.5ml/kg /hr

*Clinical Parameters: Clinical: low consciousness less than 8, plus one or more of the ff: unequal, dilated, unreactive pupils, loss of brainstem reflexes (light and oculocephalic) cranial nerve palsies III, VI and cushing's triad

** Neuroimaging Parameters: Effacement of the basal cisterns, thin, slit-like or completely obliterated ventricles, obliterated cortical sulic, shift in the midline, temporal lobe or cerebellar tonsils herniation.

Table 2. Assessment of Primary and Secondary Outcomes

Author	**Primary Outcome (Decrease in ICP)**	**GCS Score (discharge)**		**Length of Stay (days) / Duration of Coma (Hours)**		**Neurodisability/ Mortality (No. of Patients)**		**Complications**
		Mannitol	**3%HTS**	**Mannitol**	**3%HTS**	**Mannitol**	**3%HTS**	
1.Upadhyay et al. (N=200)	Difference: *Mannitol:* 7+/- 3.25 *3% Hypertonic:*11.5+/- 4.48 p <0.001 especially during the initial hours	Not specified	Not specified	Duration of Coma (Hours) *Mannitol:* 98.6 +/- 21.1 Hours *3% Hypertonic:* 77.5+/- 13.05 Hours p value<0.001		Mortality *Mannitol:* Mortality =4 *3% Hypertonic* Mortality =5 p value >0.05		No reported complications
2.Rameshkumar et al. (N=57	Difference: *Mannitol:* -5.4+/-1.7 *3% Hypertonic:*14.3+/- 1.7 p <0.001	GCS 11	GCS 13	PICU Stay (days) *Mannitol:* 19 (12.3-25.7) *3% Hypertonic:* 11 (8.4-13.6) days p value = 0.016		*Mannitol:* None: 17%, Mild 5% Moderate17%, Severe 61% Mortality =10 *3% Hypertonic* None: 39%. Mild: 13% Moderate:17, Severe 31% Mortality =6 Mortality p value= 0.21		Rebound raised ICP: Mannitol: 50%, 3%HTS: 18% Hypotension Acute Kidney Injury

3. Kumar et al. (N=30)	Difference: *Mannitol:* -7.13mmHg (SD 2.9) *3% Hypertonic:* -5.67mmHg (SD 3.9) p value = 0.33	Not specified	Not specified	PICU Stay (days) *Mannitol:* 9.5 (SD 4.3) *3% Hypertonic:* 9.64 (SD 4.4) p value= 0.92 Hospital Stay (days) *Mannitol:* 9.5 (SD 4.3) *3% Hypertonic:* 9.64 (SD 4.4) p value =0.73	Survival without disability *Mannitol:* 13 of 16 *3% Hypertonic:* 12 of 14 p value 0.69 Death of survival in vegetative state *Mannitol:* 3 (23.07%) *3% Hypertonic:* 2 (16.6%)	No reported complications
4. Vats et al. (N=43)	Difference: *Mannitol: 6.6* -8.8mmHg *3% Hypertonic:* 5.9-6.8 mmHg (p< 0.05)	Initial GCS 5 (3-9) Discharge GCS Not specified	Initial GCS 8 (3-9) Discharge GCS Not specified	Not specified	Mortality *Mannitol:* 10 of 18 *3% Hypertonic*: 12 of 25	No reported complications
5. Yildizdas et al. (N=67)	Not specified	Initial GCS 4.4 +/- 1.3 Discharge GCS Not specified	Initial 4.5+/-1.1 Discharge GCS Not specified	Duration of Coma: (hours) *Mannitol:* 123+/-48.2** *3% Hypertonic* 88.6+/- 42.5** Mannitol + 3% HTS: 87.5+/-26.1** p value =0.004	Mortality *Mannitol:* 50% *3% Hypertonic:* 25% Mannitol + 3% HTS: 20% p value =0.003	*Mannitol:* Renal failure *3% HTS:* Hyperchloremic metabolic acidosis *Cause of Mortality:* Septic shock, VAP with ARDS, Progressive Cerebral edema with pulmonary edema
6. DeCourcey et al. (N=1,632)	Not specified	Not specified	Not specified	PICU admission *Mannitol:* 784 (65.2%) *3% Hypertonic:* 269 (90%) *Mannitol + 3%HTS:* 122 (93.1%)	Mortality *Mannitol:* 31/ 1,202 (2.5%) *3% Hypertonic:* 11/299 (3.7%) Mannitol + 3% HTS: 12/131 (9.2%) p <0.001	No reported complications
7. Roumeliotis et al. (N=16)	Mannitol: 21 (17-25); 27 (22-32) p= 0.055 Hypertonic Saline: 23 (19-28); 20 (19-26) p = 0.096	Initial GCS 4 (4-4.5) Discharge GCS Not specified	Initial GCS 6 (6-7) Discharge GCS Not specified	Not specified	Mortality = 5 (31%)	No reported complications

*Converted to hours (from days) ** After 1 bolus

Risk of bias was assessed using the Cochrane Collaboration Risk of Bias assessment tool. Two separate evaluators assessed the included studies and disagreements were discussed. Our study reviewed 3 RCTs. There was low risk of selection bias for majority of the studies

included since the trials were sufficiently randomized. Low or unclear grading was noted due varying presence of blinding for personnel and assessors among different studies.

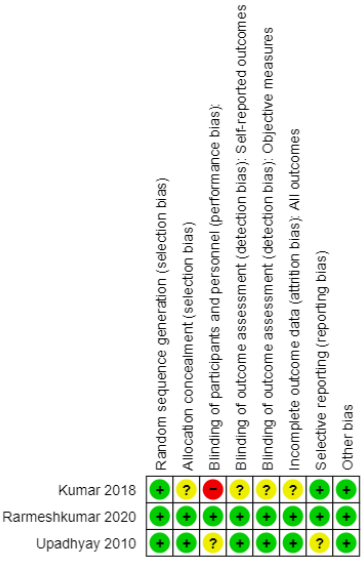

Figure 2. Risk of Bias Summary

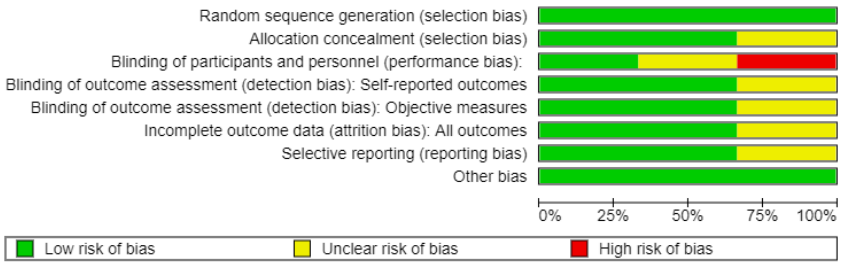

Figure 3. Risk of Bias Graph

For observational studies, the Newcastle-Ottawa Scale was used. The studies had adequate selection, with records showing ascertainment of exposure. The studies also noted proper documentation of evidence of outcomes and sufficient follow-up for outcomes.

Table 3. Newcastle-Ottawa Scale

Study	Selection	Comparability	Outcome
Vats et al. (1999)	★★★★	★	★★
Yildizdas et al. (2005)	★★	★	★★
DeCourcey et al. (2009)	★★★★	★	★★
Roumeliotis et al. (2016)	★★★	★	★★★

Study Outcomes

Two randomized controlled studies showed evidence that 3% hypertonic saline was superior to 20% mannitol in reducing raised intracranial pressure. In the prospective randomized study by in Upadhyay et al. 2010 [14] (n=200), the estimated mean difference (±SE) in ICP from baseline to 48h between the mannitol and HTS groups was significant (male: -4.6±0.06, $p<0.001$; female: -1.5±0.07, $p<0.001$). Similarly, in a recent open-label randomized trial by Rameshkumar et al. in 2020 [13] (n=57), the trend in mean ICP in the first 72 hours was significantly lower (14 ± 2 vs 22 ± 2 mmHg; p=0.009) in the hypertonic saline group. The mean change from baseline to 72 hours was significantly lower (-14.3±1.7 vs -5.4±1.7; $p \leq 0.001$) in the HTS group. Two other studies with smaller sample sizes also showed decrease in ICP but was insufficient to establish statistical significance. This was observed in the open label randomized controlled trial by Kumar et al. in 2018 [15] (n=30), the mean (±SD) reduction in ICP, was −7.13±2.9 in the mannitol group and −5.67±3.9 in HTS group; the difference was not statistically different (p=0.92). In a retrospective study by Roumeliotis et al [16] in 2016 (n=16), both mannitol and HTS were also followed by a decrease in ICP in the following 4-hour period, however, this did not achieve statistical significance (mannitol p= 0.055 and HTS, p=0.096). Due limited number of studies and high heterogeneity, a pooled analysis could not be done.

In a recent retrospective cohort study by Rameshkumar et al (2020), the median m-GCS score upon discharge from the PICU in the HTS group was 13 (IQR=10 to 14) and 11 (IQR=3 to 13) in the mannitol group. Test of independence of distributions between the two groups showed that GCS scores in the saline group were significantly higher than in the mannitol group (p=0.006). Although baselinescores were reported in 3 of 7 studies, no other study reported GCS score upon discharge.

Of 332 cases of increased intracranial pressure treated with either 20% mannitol or 3% hypertonic saline, duration of coma or length of stay in PICU was significantly shorter in the saline group than in the mannitol group (SMD=0.68, 95% CI=0.17 to 1.17, p=0.008).

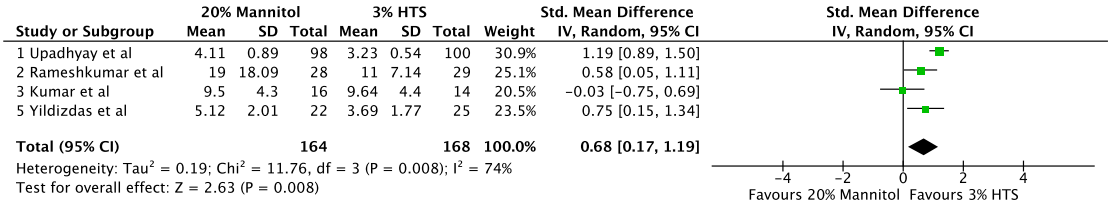

FIGURE 4. Forest plot on the duration of coma or stay in PICU (in days) between 20% Mannitol and 3% Hypertonic saline in children with increased intracranial pressure

Of 1,876 cases of patients with increased intracranial pressure, 285 were randomly treated with either 20% Mannitol or 3% hypertonic saline. Mortality in these groups were comparable. The pooled risk of mortality using 3% hypertonic saline compared to 20% mannitol was 1.36 (95% CI: 0.70 to 2.62, p=0.36). In comparison to a fixed effects model, there was no substantial change in the pooled RR and although the 95% confidence intervals narrowed, mortality rate was still comparable between the two groups (RR=1.31, 95% CI: 0.68 to 2.52, p=0.42). Similar results were observed on the 1,591 cases treated with either 20% Mannitol or 3%

hypertonic saline (RR=1.07, 95% CI: 0.72 to 1.59, p=0.730).

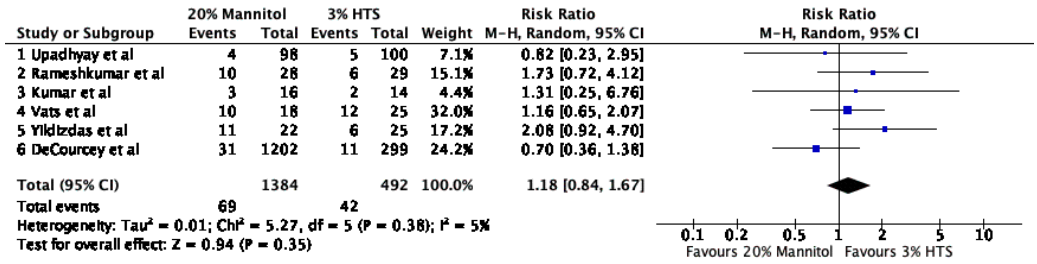

FIGURE 5. Forest plot on relative risk of mortality between 20% Mannitol and 3% Hypertonic saline in children with increased intracranial pressure

No complications were reported in 5 of 7 studies. In an open label randomized trial by Rameshkumar et al. in 2020, there was a significantly higher proportion of patients who developed rebound increase in intracranial pressure in the mannitol group than in the hypertonic saline group (50% vs 18%, RR=0.42, 95% CI=0.19 to 0.92). In the same study, they also reported a lower number of patients experiencing hypotension in the hypertonic saline group as compared to the mannitol group. They also reported the occurrence of acute kidney injury and hemolysis, which was comparable between the two groups. In a retrospective study by Yildizdas et al. [17] in 2006, one patient developed renal failure. Treatment with mannitol was then discontinued. One patient from the hypertonic saline group also developed diabetes insipidus, hence treatment was also discontinued. In the same study, an equal number of patients, two from each group, developed hyperchloremic metabolic acidosis. No serious adverse events were associated with the trial interventions.

DISCUSSION

Osmotherapy plays a vital role in the management of increased intracranial pressure. Being the most available osmotherapeutic agents in our setting, the

study compared 20% mannitol and 3% hypertonic saline. The investigators reviewed available articles and noted that studies on the osmotherapeutic treatment for this neurologic emergency proved to be limited especially in the pediatric age group. Majority of the available studies were done in the adult population with severe traumatic brain injury as the cause for increased ICP.

In terms of reduction in intracranial pressure, there is evidence showing increased benefit of using 3% hypertonic saline over 20% Mannitol. Compared with majority of the previously available studies which focused primarily on traumatic brain injury, the study population assessed in both studies showed varying etiologies causing cytotoxic, vasogenic, interstitial edema or a combination ultimately resulting to increased intracranial pressure. Osmotic diuretics, such as mannitol, alter the starling forces promoting the movement of fluid from the cell reducing intracellular volume and subsequently decreasing intracranial pressure.[18] An intact blood brain barrier enables the maintenance of this gradient. In central nervous system infections such as meningitis, cytokines and other immune cells circulate and affect endothelial cells leading to changes and increased permeability of the blood brain barrier [19]. Similarly, clinical studies on infants with previous hypoxic injury was also noted with increased albumin/ CSF blood ratios suggesting changes in barrier integrity.[20] In the two RCTs assessed, of which majority of the subjects were diagnosed with CNS infections such as viral meningoencephalitis and bacterial meningitis, a better response was seen with the use of hypertonic saline in decreasing intracranial pressure between 48-72 hours. Apart from an infectious cause, a large retrospective study in our review included children diagnosed with cerebral edema due to Diabetic Ketoacidosis. In the study, outcome comparison was made in terms of PICU stay and mortality. Actual decrease in ICP measurement was not

reported. Other etiologies in our review also included patients with hemorrhage, anoxia, infarction, trauma as well as tumors. In terms of effective dose, this study showed that within the therapeutic range, decrease in ICP was seen after administration of 20% mannitol and 3% hypertonic saline. In half of the studies assessed, 20% mannitol and 3% hypertonic saline were both given as bolus and were noted to be of equal dose. Full assessment of appropriate dose titration, manner of infusion and frequency in the various studies however was limited by the differences in available data such as serum osmolality, electrolyte levels, neurologic examination status as well as type of ICP monitoring done. The availability of these laboratory tests and monitoring modalities may also vary among different institutions.

Majority of the studies in the review utilized a bolus infusion for delivering both mannitol and hypertonic saline. Two retrospective studies in the adult population diagnosed with traumatic brain injury compared the method of 3% hypertonic saline infusion and showed varied results. In a 9-year retrospective study by Roquilly et al, 2011 [21], use of continuous controlled infusion showed increase in cerebral perfusion pressure (CPP) and resultant decreased in intracranial pressure. In another retrospective study by Maguigan et al, 2017 [22] more patients given continuous infusion reached the goal serum osmolality compared with bolus administration. However, for their study, there was no statistically significant difference in the CPP and ICP between the two methods of infusion. In the review, the study by Rameshkumar et al (2020) showed use of mannitol delivery in boluses every 4 hours. On the other hand, 3% hypertonic saline was initially given via bolus and was then maintained via continuous infusion. In the study, use of hypertonic saline in this manner resulted in a statistically significant decrease in ICP.

Different complications have been associated with the use of 20% mannitol and 3% hypertonic saline. In the review, hypotension and renal failure was seen in several patients who were previously given mannitol while diabetes insipidus was seen in a patient who was previously given hypertonic saline. In the two studies that reported complications, acute kidney injury, hemolysis and hyperchloremic metabolic acidosis developed in patients under both treatment arms. A retrospective study by Gonda et al in 2013 assessed the level of hypernatremia in prolonged hypertonic saline infusions as well as its complications. In their study including eighty-eight children, they noted that children with sustained serum sodium of >170, compared with those with serum sodium of 150-160 meq/L, had a high occurrence of thrombocytopenia ($p< 0.001$), renal failure ($p< 0.001$) as well as neutropenia and acute respiratory distress syndrome.[23] Comparing this finding with the current review, one RCT study reported complications at serum levels of 141+/- 7 for the mannitol group and 144+/-8 for the hypertonic saline group. In the study by Yildizdaz et al, serum sodium ranged from 144-176meq/L. These support the need for caution in the use of osmotherapy as well as the need for adequate monitoring while titrating to reach adequate osmolality to maximize decompressive effects in children with increased intracranial pressure.

Limitations to the study include the following: (1) few numbers of randomized control trials, comparing the two osmotherapeutic agents in the pediatric age group (2) current available studies have different outcome measures; and (3) there were differences in ICP monitoring and measurements, diagnostics, tools utilized and interventions.

CONCLUSION

This systematic review assessed available literature on the effectiveness of 20% Mannitol and 3% Hypertonic saline in the management of increased ICP in the pediatric

age group. The investigators noted that while both agents showed favorable effects in lowering intracranial pressure caused by varying etiologies, hypertonic saline showed benefit compared with 20% mannitol. While more developed hypotension and rebound increase in ICP with the use of mannitol, both agents reported occurrences of acute kidney injury, hemolysis and hyperchloremic metabolic acidosis. Due to the limited number of articles and heterogeneity of the studies reviewed, no firm conclusions can be made regarding the superiority of one agent over the other. Larger prospective randomized studies in different clinical situations using 20% mannitol and 3% hypertonic saline in the treatment of increased ICP in the pediatric age group are needed to render valid affirmations.

REFERENCES:

1. Swaiman KF, Ashwal S, Ferriero D. Swaiman's Pediatric Neurology. Sixth Edition. New York: Elsevier. 2018.
2. Ferguson NM, Shein SL, Kochanek PM, et al. Intracranial Hypertension and Cerebral Hypoperfusion in Children with Severe Traumatic Brain Injury: Thresholds and Burden in Accidental and Abusive Insults. Pediatric Critical Care Medicine. 2016. 17(5): 444
3. Kochanek PM, Tasker RC, Bell MJ et al. Management of Pediatric Severe Traumatic Brain Injury: 2019 Consensus and Guideline Based Algorithm for First and Second Tier Therapies. Society of Critical Care Medicine. March 2019. Volume 20. Number 3.
4. Freeman, WD. Management of Intracranial Pressure. Minneapolis Minnesota: Continuum Journal. American Academy of Neurology. 2015; 21 (5): 1299-1323.
5. Zhang W, Neal J, Liang L et al. Mannitol in Critical Care and Surgery Over 50+ years: A Systematic Review

of Randomized Control Trials and Complications with Meta-Analysis. Neurosurgical Anesthesiology. 2019 Jul;31(3):273-284

6. Cook AM, Jones GM, Hawryluk GW et al. Guidelines for the Acute treatment of Cerebral edema in Neurocritical Care patients. Neurocritical Care. (2020)32: 647-666.
7. Witherspoon B, Ashby NE. The use of Mannitol and Hypertonic Saline Therapies in patients with Elevated Intracranial Pressure: A Review of Evidence. Nursing Clinics of America. 2017. Jun;52(2):249-260.
8. Alnemari AM, Krafcik BM, Mansour TR et al. A Comparison of Pharmacologic Therapeutic Agents Used for the Reduction of Intracranial Pressure After Traumatic Brain Injury. World Neurosurgery. 2017 Oct; 106:509-528
9. Sabers EJ, Reiter PD, Skillman HE et al. . Concentrated Hypertonic Saline in Severe Pediatric Traumatic Brain Injury. Brain Injury. 2020 May 11; 34(6): 828-833.
10. Mangat HS, Chiu YL, Gerber LM et al. Hypertonic Saline reduces cumulative and daily intracranial pressure burdens after severe brain injury. Journal of Neurosurgery. 2015 Jan; 122 (1): 202-10
11. Khanna S, Davis D, Peterson B et al. Use of Hypertonic Saline in the treatment of Severe Refractory Posttraumatic Intracranial Hypertension in Pediatric Traumatic Brain Injury. Critical Care Medicine. 2000 Apr. 28 (4): 1141-51.
12. Kamel H, Navi BB, Nagawa K et al. Hypertonic Saline Hypertonic Saline versus Mannitol for the treatment of Intracranial Pressure: A meta-analysis of randomized control trials. Critical

Care Medicine. 2011 March. Vol 39. No 3.

13. Rameshkumar R, Bansal A, Singhi S et al. Randomized Clinical Trial of 20% Mannitol Versus 3% Hypertonic Saline in Children with Raised Intracranial Pressure Due to Acute CNS Infections. Neurocritical Care. 2020, Dec 21 (12): 1071-1080
14. Upadhyay P, Tripathi VN, Singh RP et al. Role of hypertonic saline and mannitol in the management of raised intracranial pressure in children: A randomized comparative study. Journal of Pediatric Neuroscience. 2010 Jan;5(1):18-21.
15. Kumar SA, Devi BI, Reddy M et al. Comparison of equiosmolar dose of hyperosmolar agents in reducing intracranial pressure—a randomized control study in pediatric traumatic brain injury. Child's Nervous System, 2019. 35, 999-1005
16. Roumeliotis N, Dong C, Pettersen G et al. Hyperosmolar therapy in pediatric traumatic brain injury: a retrospective study. Child's Nervous System. 2016 Dec;32(12):2363-2368.
17. Yildizdaz D, Altunbasak S, Celik U et al. Hypertonic Saline Treatment in Children with Cerebral Edema. Indian Pediatrics. 2006. Sep;43(9):771-9. https://pubmed.ncbi.nlm.nih.gov/17033115/
18. Katzung, B. Basic and Clinical Pharmacology. Fourteenth Edition. 2018.
19. Menke, J, Sarnat HB, Maria BL. Child Neurology, Sixth Edition. Philadelphia: Lippincott Williams and Wilkins. 2000.
20. Mallard C, Ek CJ, Vexler ZS. The myth of the immature barrier systems in the developing brain: role in perinatal injury. Journal of Physiology. 596.23 (2018) pp 5655–5664

21. Roquilly A, Mahe PJ, Latte DD et al. Continuous controlled-infusion of hypertonic saline solution in traumatic brain-injured patients: a 9-year retrospective study. Critical Care, 2011. R260.
22. Maguigan KL, Dennis BM, Hamblin SE et al. Method of Hypertonic Saline Administration: Effects on Osmolality in Traumatic Brain Injury Patients. Journal of Clinical Neuroscience. 2017 May 39: 147-150
23. Gonda DD, Meltzer HS, Crawford JR et al. Complications Associated With Prolonged Hypertonic Saline Therapy in Children With Elevated Intracranial Pressure. Neurocritical care. 2013 July; 14(6): 610-20