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Comparision between 3% Hypertonic Saline and 20% Mannitol in the Management of Raised Intracranial Pressure in Children

[1] Sristi Upadhyay, [2] Jyoti Agrawal, [3] Shyam Kafle, [4] Sagar Devkota, [5] Manju Shrestha
[1, 2, 3, 5] Department of Pediatrics and Adolescent Medicine, B P Koirala Institute of Health Sciences, Dharan, Nepal
[4] Department of Anesthesiology and Critical Care, Kulhudhuffushi Regional Hospital, Maldives

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Corresponding Author: **Sagar Devkota**

Abstract

Background

Osmotic agents like mannitol and hypertonic saline are the mainstay of management of raised intracranial pressure (ICP) along with non-pharmacological measures like head elevation, hyperventilation, and hypothermia and CSF drainage. Several recent studies have shown hypertonic saline relatively superior to mannitol however, both are being used commonly. So, this study was done to compare the efficacy of mannitol and hypertonic saline in management of raised ICP in children.

Methods

This was a prospective randomized comparative study done among 40 children aged 1-5 years admitted in department of Pediatrics and Adolescent Medicine, BPKIHS, Dharan with clinical signs and symptoms of raised ICP They were divided into two groups based on consecutive sampling with group 1 receiving 20% mannitol and group 2 receiving 3% hypertonic saline.

Results

Both the groups were comparable for age distribution, gender and baseline characteristics. Pretreatment mean MAP was higher in group 2 as compared to group 1 while decrease in MAP was present in both groups at 24, 36-, 48-, 56- and 60-hours post-treatment; however, this was not statistically significant. 78.9% cases improved with mannitol while 90.5% improved with 3% hypertonic saline but this was not statistically significant.

Conclusion

Hypertonic saline can be an equally effective agent for management of raised ICP in children but larger and multi-centric study may help in determining which one is better.

Keywords: Children, Hypertonic Saline, Intracranial Pressure, Mannitol, Mean Arterial Pressure

Introduction

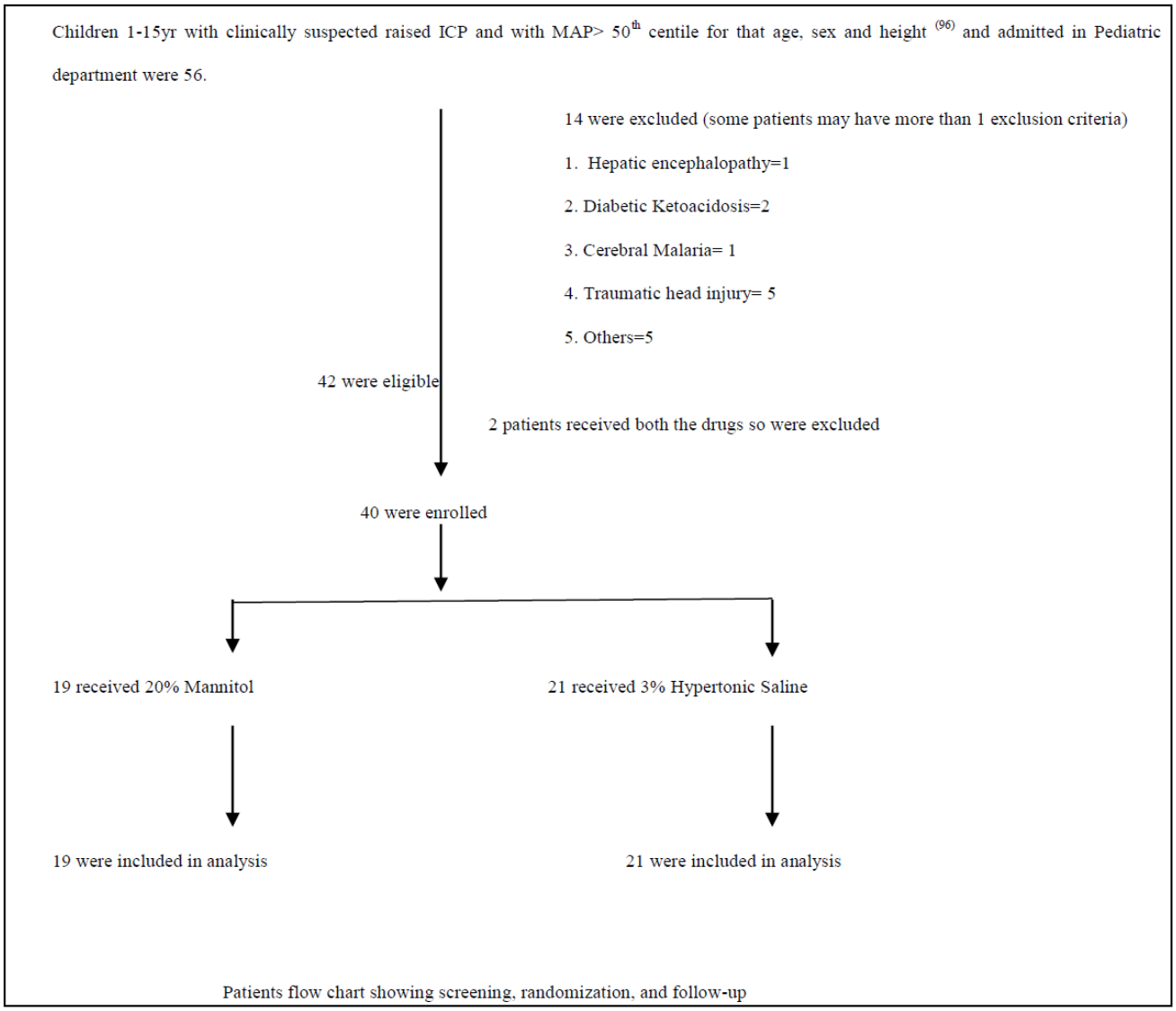
Management of raised intracranial pressure (ICP) is aimed at optimizing cerebral perfusion pressure and oxygen supply to the brain as it is known to one of the major causes of morbidity and mortality if not treated successfully [1-5]. Apart from non-pharmacological treatment, role of osmotherapy is based on the principle that the osmotic agents will lower ICP by creating an osmotic gradient by increasing osmotic pressure of plasma [6]. Osmotic agents include mannitol, urea, glycerol and hypertonic saline but urea and glycerol were abandoned because of their low efficacy. Among the hyperosmolar agents, mannitol and hypertonic saline (HTS) have been commonly used for lowering ICP but evidences for the better one among the two is still lacking [8-11] Therefore, we conducted this study to compare the efficacy of HTS over mannitol taking into consideration the changes in MAP with the use of these drugs as a marker for ICP reduction.

Methods

This was a randomized comparative study carried out in pediatric ward and pediatric intensive care unit of Department of Pediatrics and Adolescent Medicine, BPKIHS, Dharan over a period of one year. Forty children aged 1-15 years admitted in department of Pediatrics with clinical signs and symptoms of raised ICP and MAP above 50th centile considered for that age, sex and height were included in the study [12]. Consecutive sampling technique was used to conduct the study. Patients were randomized into two statistically comparable groups using a computer-generated random number sampling with 1:1 allocation

into two groups. Group 1 was treated with 20% mannitol and Group 2 was treated with 3% hypertonic saline. Number of cases in group 1 was 19 and group 2 was 21. Single blinding was done as patients were unaware of which treatment was being provided.

In both groups, a loading dose was given at the rate of 5ml/kg followed by maintenance dose of 2ml/kg every 6 hourly for maximum of two days (48 hours).



Patients flow chart showing screening, randomization, and follow-up

Demographic data were recorded. pre- and post-intervention symptoms and signs were recorded. Pre- intervention vital parameters – respiratory rate (RR), heart rate (HR), Glasgow Coma Scale (GCS) and neurological examination were recorded and then post intervention parameters at 6 hours, 12 hours, 24 hours, 36 hours, 48 hours, 54 hours and 60 hours of initiation of treatment were recorded.

CSF examination was mandatory in all cases with signs of meningeal irritation and CT/MRI was done as per institutional protocol. Comparison of decrease in MAP in both groups was done at 6, 12-, 24-, 36- and 48-hours following administration of 20% mannitol and 3% hypertonic saline. Common adverse effects following use of 20% mannitol and 3% hypertonic saline in the management of raised ICP such as hypernatremia, hyperosmolarity, AKI and rebound increase in MAP were recorded.

Ethics

Ethical clearance was obtained from ethical review committee of B P Koirala Institute of Health Sciences.

Statistical Analysis

Data was entered, cleaned and coded in MS Excel 2010 and converted it into SPSS 11.5 version for statistical analysis.

For Descriptive Statistics: Percentage, Mean, Standard Deviation and proportion was calculated and graphical and tabular presentation was done.

For Inferential Statistics: Independent t- test (student t test) was applied to find out the significant difference in MAP, and mortality between Group 1 and Group 2 at 95% CI where $p < 0.05$ was considered statistically significant.

Results

A total of 40 children of age between 1-15 years were enrolled in the study after taking informed consent from the parents and they were randomized into two groups. Group 1 was treated with 20% Mannitol and group 2 was treated with 3% hypertonic saline. Number of children in group 1 was 19 and group 2 was 21. Among the 40 cases, majority of cases were from age group of 1-5 years (55%) followed by 6-10 years (27.5%) and 17.5% cases were between 11-15

years. Mean age ± SD in Group1 was 6.06 ± 3.95 years and Group 2 was 5.78 ± 4.50 years.

Comparison of clinical features at the time of presentation between two groups

The clinical features at the time of presentation were comparable between the two groups (p>0.05) (Table 1). Both groups were comparable in terms of presenting symptoms. In group 1, vomiting was the predominant symptom in 89.4% followed by fever 84.2%, headache 84.2%, irritability 42.1%, seizure 36.8%, lethargy 26.3% and poor feeding 15.8%. Irritability, lethargy, seizure and poor feeding were more in Group 2. However, the difference was not statistically significant. Overall, out of 40 cases, fever was the commonest symptom present in 90% of cases followed by vomiting in 87.5%, headache in 75%, seizure in 47.5%, irritability was present in 47.5%, altered sensorium (GCS< 14) in 45%, lethargy and poor feeding were present in 30% and 22.5% respectively.

Table 1: Comparison of baseline characteristics between two groups

	Group 1 (19)	Group 2 (21)	p value
Presenting Symptoms			
Fever	16(84.2%)	20(95.2%)	0.33
Headache	16(84.2%)	14(66.6%)	0.28
Vomiting	17(89.4%)	18(85.7%)	1.00
Irritability	8(42.1%)	11(52.4%)	0.54
Lethargy	5(26.3%)	7(33.3%)	0.73
Seizure	7(36.8%)	12(57.1%)	0.22
Poor feeding	3(15.8%)	6(28.5%)	0.45
Clinical signs at admission			
Signs of Meningeal irritation	13(68.4%)	14(66.6%)	1.00
Pretreatment mean MAP	78.693±9.489	80.649±10.624	0.544
GCS category			0.26
3-8	1	3	
9-12	3	2	
13-14	3	5	
Admission GCS=15	12(30%)	10(25%)	

Clinical Outcome

MAP before starting the treatment and post intervention at 6, 12, 24, 36, 48, 54 and 60 hours was measured in both groups. MAP at 54 and 60 hours was measured to see the rebound rise in ICP after stopping the hyperosmolar therapy at 48 hrs. Then the mean pre-MAP of both groups was compared with mean post treatment MAP at 6, 12, 24, 36, 48, 54 and 60 hrs. Pretreatment mean MAP was higher in group 2 in comparison to group 1 however the difference was not significant statistically. At 6 hours of post treatment, mean MAP was increased in group 1 whereas in group 2 it was almost same as pretreatment. At 12 hours of post treatment, mean MAP was decreased in group 1 but it was increased in group 2. Thereafter, decrease in mean MAP was also found in both groups at 24, 36, 48, 54 and 60 hours in comparison to pretreatment mean MAP. However, there was no statistically significant difference between treatment group 1 and 2. (Table 2)

Table 2: Relationship of mean MAP between pre and post drug at definite time intervals between Group 1 and Group 2

Hours	Group 1 (Mean ± SD)	Group 2 (Mean ± SD)	p value	Significance
Pre treatment	78.693±9.489	80.649±10.624	0.544	NS
6	79.639±9.761	80.649±8.937	0.735	NS
12	78.588±8.745	80.744±10.209	0.480	NS
24	76.379±9.207	78.968±9.870	0.398	NS
36	73.820±6.879	76.114±9.983	0.408	NS
48	72.874±6.858	75.543±8.375	0.280	NS
54	72.531±6.945	74.800±8.037	0.348	NS
60	72.331±7.035	74.314±7.916	0.410	NS

In group 1, mean MAP was slightly increased at 6 hours and thereafter there was decrease in mean MAP at 12, 24, 36, 48, 54 and 60 hours. The decrease in mean MAP was significant at 36 hour and highly significant at 48, 54 and 60 hours. In group 2, mean MAP at 6 hours was equal to that of Pre-treatment and at 12 hours mean MAP was increased slightly which was not significant. Thereafter, the decrease in mean MAP at 36, 48, 54 and 60 hours was significant. However, there was no statistically significant difference between treatment group 1 and 2 in mean of difference between pre and post treatment mean MAP at 6, 12, 24, 36, 48, 54 and 60 hours. In treatment group 1, post treatment MAP at 6 hours was increased by 0.946 which was not significant. Thereafter, post treatment MAP decreased over 60 hours of observation. However, the decrease was not significant at 12 and 24 hours and it was highly significant at 36, 48, 54 and 60 hours. (Table 3) In treatment group 2, there was no change in post treatment MAP at 6 hours but it was increased by 0.095 at 12 hrs which was not significant. Thereafter, there was decrease in post treatment MAP at 24, 36, 48, 54 and 60 hrs. The decrease in MAP was not significant at 24 hours but was significant at 36 hours and highly significant at 48, 54 and 60 hours. (Table 4)

Table 3: Relationship of mean of difference between pre and post drug mean MAP at definite time intervals (Group 1)

Hours	Mean difference	p- value	Significance
6	+0.946	0.534	NS
12	-0.105	0.940	NS
24	-2.313	0.059	NS
36	-4.872	0.002	**HS**
48	-5.818	0.001	**HS**
54	-6.161	0.001	**HS**
60	-6.361	0.001	**HS**

Table 4: Relationship of mean of difference between pre and post drug mean MAP at definite time intervals (Group 2)

Hours	Mean difference	p-value	Significance
6	+0.00	1.00	NS
12	+0.095	0.949	NS
24	-1.680	0.334	NS
36	-4.535	0.022	**S**
48	-5.106	0.007	**HS**
54	-5.849	0.003	**HS**
60	-6,335	0.002	**HS**

Treatment Outcome

Out of 19 cases in Group 1, 15 (78.9%) cases improved with Mannitol and among 21 cases in Group 2, 19 (90.5%) cases improved with 3% Hypertonic Saline but this was not found to be statistically significant (p value 0.64) (Table 5).

Table 5: Association of treatment used and the outcome of the treatment

Outcome	Group 1	Group 2	P-value
Improved	15 (78.9%)	19(90.5%)	0.64
Not improved	4 (21.1%)	2 (9.5%)	

Discussion

In our study, out of 40 cases, 55% were of age group 1-5 years. The mean age ± SD in Group 1 was 6.06 ± 3.95 years and Group 2 was 5.78 ± 4.50 years which was similar to the study done in India by Upadhyay *et al* [12] which had mean age of 5.65 years in 20% Mannitol group and 5.7 years in 3% HS group. In our study, the proportions of the male and female participants were almost equal, Group 1 had 52.6% male and Group 2 had 52.4%, M: F ratio being 1.1:1 in both groups. In contrast, male preponderance was observed in study by Upadhyay *et al* [12], M: F ratio being 1.45:1 and 1.5:1 in mannitol group and 3%HS group respectively. In our study, fever was the commonest symptom which was noted in 90% of patients followed by vomiting (87.5%), headache (75%), convulsion (47.5%), irritability (47.5%), altered sensorium (45%), lethargy (30%), and poor feeding (22.5%). Out of 40 enrolled patients with raised ICP, 4 patients (7.5%) had focal neurological deficit and 67.5% of patients had signs of meningeal irritation, predominantly in the age group of 11-15 years. Similar observation was reported in the study done by Farag HF *et al* [13] in 2005 among age ranged from 3 months to 15 years, where the predominant symptoms of acute CNS infections were high fever (92.1%), vomiting (75.2%), and seizures (64.9%). Meningeal signs, cranial nerve palsies and coma were elicited in 23.6%, 16.8% and 11.9% of cases respectively. For those below one year old, irritability and refusal of feeds were encountered among 92.9% and 78.6% respectively.

In a study by Minns RA *et al* [14], the incidence of raised intracranial pressure in comatose children was 100% with mass lesion; 80% with hydrocephalus; 66% with meningitis; 57% with encephalitis; 53% of those with head injuries; 23% with anoxic ischemic damage. In 1988, the study by Reboud P *et al* [15] observed raised ICP in 86% of cases with meningitis and 69% cases of encephalitis.

In our study, there was significant decrease in mean MAP in both groups at 36 and 48 hours in comparison to pre-treatment mean MAP. However, the difference between treatment group 1 and 2 in mean of difference between pre and post drug mean MAP at 6, 12, 24, 36 and 48 hours was not statistically significant. Similarly, a study done in France by Francony G *et al* [16] showed that the ICP in both groups was significantly reduced (45 and 35%, respectively) at 60 min from the start of infusion, which showed no differences in the degree of ICP reduction between the two agents and was not statistically significant. In contrast to our study, a retrospective comparison of Hypertonic Saline and Mannitol in Head-Injured Patients with raised Intracranial Pressure Undergoing Decompressive Craniectomy showed that the slope of the reduction in ICP in response to a bolus dose at baseline was higher with HTS than with mannitol [17]. In contrast, the study done in India showed that decrease in MAP was highly significant ($p< 0.001$) at 0 hour in males 0,6 hour in females, and moderately significant at 12 and 36 hours in females and significant ($p<0.05$) at 6,24 and 42 hours in males with 3% Hypertonic Saline group. Decrease in coma hours was a highly significant finding in 3% Hypertonic Saline group. However, there was no difference in mortality [12].

Another prospective open label RCT between 20% Mannitol and 3% Hypertonic Saline in Children aged 1-12 years with raised ICP due to acute central Nervous System infections done in PIGMER by Ramesh K R *et al* [18] had shown significant reduction in mean ICP (14 vs. 22 mmHg, $p=0.010$) at 72-hrs in HTS group as compared to mannitol-group. HTS successfully controlled raised ICP in 79% of patients, in contrast to 50% by mannitol (RR=0.63, 95% CI 0.42–0.95; $p=0.020$).

In a prospective, randomized study between isovolumetric hypertonic solutes in the treatment of refractory post-traumatic intracranial hypertension by Vialet R *et al* [19] showed that 7.5% HS was more effective than 20% mannitol in reducing ICP. Similarly, another prospective study conducted by Horn *et al* [20], using 7.5 % HS administered as bolus infusion to patients with elevated ICP secondary to trauma and not responding to standard treatment showed that it was effective in reducing ICP. A 2010 systematic review and meta-analysis by Mortazavi *et al* [21] included 36 studies (10 prospective RCTs, 1 prospective and nonrandomized trial, 15 prospective observational trials, and 10 retrospective studies) and concluded that hypertonic saline was more effective than mannitol at reducing ICP with odds ratio of 0.36 (0.19-068; $p=0.002$). However, the analysis was limited by low number of patients, limited RCTs, and inconsistent methods between studies.

Table 6: Various studies comparing hyperosmolar therapy (Mannitol vs HTS) in raised ICP

Author & year	Study Design	Age	No. of patients	Intervention	Results
Vats, *et al*. 1999 [22]	Retrospective Study	9months-16 years	43	I- 20% Mannitol (n=18) II- 3% HTS (n=25)	Significant reduction in ICP at 30-, 60- and 120-min following HS. Significant ICP reduction at 60 and 120 min after receiving mannitol. ICP of the patient's receiving mannitol was significantly higher than those receiving HS at 60 and 120 min.
Fisher B *et al* 2000 [23]	Retrospective cohort review	avg. 8 years	68	3% HTS	HS effectively lowered ICP and ICP was under good control majority of the time.
Khanna *et al* 2000 [24]	Prospective	4months-13 years (mean 5.7 years)		Continuous infusion of 3% HTS on refractory ICH	Significant decrease in ICP spike frequency at 6,12,24,48 and 72hrs.($p < 0.001$)
Yildizdas D *et al* 2006 [25]	Retrospective study	1-180 months	67	I- Mannitol II- HTS III- either HTS+ Mannitol or HTS after mannitol has stopped.	In group II and group III, duration of comatose state and mortality rate were significantly lower. ($p < 0.05$)
Upadhyay *et al* 2008 [12]	Prospective Randomized study	2-18 years	200	I- 20% Mannitol II- 3% HTS III- S. osmolarity >320 treated with 3% HS	Decrease in MAP was highly significant ($p < 0.001$) at 0hr Male, 0, 6 hr Female; moderately significant at 12,36 hr in female and significant ($p<0.05$) at 6,24.48hr in 3% HS group.
Rameshkumar R 2020 [18]	Randomized clinical trial	1-12 years	57	I- 20% Mannitol II- 3%Hypertonic Saline	Mean (± SE) reduction of intracranial pressure (-14.3 ± 1.7 vs -5.4 ± 1.7 mm Hg; $p \leq 0.001$) and elevation of cerebral perfusion pressure (15.4 ± 2.4 vs 6 ± 2.4 mm Hg; $p = 0.007$) from baseline were significant in hypertonic saline-group

Conclusion

Based on this study, significant decrease in MAP was found in both groups at 36 hours and 48 hours after initiation of the treatment. However, there was no statistically significant difference between treatment group 1 and 2 in mean of difference between pre and post drug mean MAP at 6, 12, 24, 36 and 48 hours. Even after stoppage of hyperosmolar therapy at 48 hours, there was no rebound increase in MAP in both groups at 54 and 60 hours rather there was significant decrease in comparison to pretreatment MAP. Similarly, out of 19 cases, 15 (78.9%) cases improved with 20% mannitol and among 21 cases, 19 (90.5%) cases improved with 3% Hypertonic Saline but this difference was not statistically significant. Therefore, 3% HTS is as can be used an equally effective agent as 20% mannitol in the management of raised ICP. However, this needs to be confirmed with larger randomized controlled trials. A larger and multicentric study may help in determining the optimum dose and concentration of HTS that will be most effective in reducing raised ICP because of the very small size and indirect measurement of ICP.

References

1. Ramesh Kumar R, Singhi SC, Singhi P. Raised intracranial pressure (ICP): Management in emergency department. Indian J Pediatr. 2012; 79(4):518-524. Doi: 10.1007/s12098-011-0648-x
2. Gillson N, Jones C, Reem RE, Rogers DL, Zumberge N, Aylward SC. Incidence and Demographics of Pediatric Intracranial Hypertension. Pediatr Neurol. 2017; 73:42-47. Doi: 10.1016/j.pediatrneurol.2017.04.021
3. Treggiari MM, Schutz N, Yanez ND, Romand JA. Role of intracranial pressure values and patterns in predicting outcome in traumatic brain injury: A systematic review. Neurocrit Care. 2007; 6(2):104-112. Doi: 10.1007/s12028-007-0012-1
4. Solomon T, Dung NM, Kneen R, Thao le TT, Gainsborough M, Nisalak A, *et al*. Seizures and raised intracranial pressure in Vietnamese patients with Japanese encephalitis. Brain. 2002; 125(Pt 5):1084-1093. Doi: 10.1093/brain/awf116
5. Durand ML, Calderwood SB, Weber DJ, Miller SI, Southwick FS, Caviness VS Jr, *et al*. Acute bacterial meningitis in adults: A review of 493 episodes. N Engl J Med. 1993; 328(1):21-28. Doi: 10.1056/NEJM199301073280104
6. Fink ME. Osmotherapy for intracranial hypertension: Mannitol versus hypertonic saline. Continuum (Minneap Minn). 2012; 18(3):640-654. Doi: 10.1212/01.CON.0000415432.84147.1e
7. Lassen NA, Agnoli A. The upper limit of autoregulation of cerebral blood flow--on the pathogenesis of hypertensive encepholopathy. Scand J Clin Lab Invest. 1972; 30(2):113-116. Doi: 10.3109/00365517209081099
8. Knapp JM. Hyperosmolar therapy in the treatment of severe head injury in children: Mannitol and hypertonic saline. AACN Clin Issues. 2005; 16(2):199-211. Doi: 10.1097/00044067-200504000-00011
9. Worthley LI, Cooper DJ, Jones N. Treatment of resistant intracranial hypertension with hypertonic saline. Report of two cases. J Neurosurg. 1988; 68(3):478-481. Doi: 10.3171/jns.1988.68.3.0478
10. Bermueller C, Thal SC, Plesnila N, Schmid-Elsaesser R, Kreimeier U, Zausinger S. Hypertonic fluid resuscitation from subarachnoid hemorrhage in rats: A comparison between small volume resuscitation and mannitol. J Neurol Sci. 2006; 241(1-2):73-82. Doi: 10.1016/j.jns.2005.10.016
11. Engorn B, Flerlage J. The Harriet Lane Handbook. 20th ed. Philadelphia: Elsevier Saunders, 2015, 129-135.
12. Upadhyay P, Tripathi VN, Singh RP, Sachan D. Role of hypertonic saline and mannitol in the management of raised intracranial pressure in children: A randomized comparative study. J Pediatr Neurosci. 2010; 5(1):18-21. Doi: 10.4103/1817-1745.66673

13. Farag HF, Abdel-Fattah MM, Youssri AM. Epidemiological, clinical and prognostic profile of acute bacterial meningitis among children in Alexandria, Egypt. Indian J Med Microbiol. 2005; 23(2):95-101. Doi: 10.4103/0255-0857.16047
14. Minns RA. Problems of intracranial pressure in childhood. Clinics in developmental medicine 113/114. London: MacKeith Press, 1991, 1-458.
15. Rebaud P, Berthier JC, Hartemann E, Floret D. Intracranial pressure in childhood central nervous system infections. Intensive Care Med. 1988; 14(5):522-525. Doi: 10.1007/BF00263524
16. Francony G, Fauvage B, Falcon D, Canet C, Dilou H, Lavagne P, *et al*. Equimolar doses of mannitol and hypertonic saline in the treatment of increased intracranial pressure. Crit Care Med. 2008; 36(3):795-800. Doi: 10.1097/CCM.0B013E3181643B41
17. Cheng F, Xu M, Liu H, Wang W, Wang Z. A Retrospective Study of Intracranial Pressure in Head-Injured Patients Undergoing Decompressive Craniectomy: A Comparison of Hypertonic Saline and Mannitol. Front Neurol. 2018; 9:631. Doi: 10.3389/fneur.2018.00631
18. Rameshkumar R, Bansal A, Singhi S, Singhi P, Jayashree M. Randomized Clinical Trial of 20% Mannitol Versus 3% Hypertonic Saline in Children with Raised Intracranial Pressure Due to Acute CNS Infections. Pediatr Crit Care Med. 2020; 21(12):1071-1080. Doi: 10.1097/PCC.0000000000002557
19. Vialet R, Albanèse J, Thomachot L, Antonini F, Bourgouin A, Alliez B, *et al*. Isovolume hypertonic solutes (sodium chloride or mannitol) in the treatment of refractory posttraumatic intracranial hypertension: 2 mL/kg 7.5% saline is more effective than 2 mL/kg 20% mannitol. Crit Care Med. 2003; 31(6):1683-1687. Doi: 10.1097/01.CCM.0000063268.91710.DF
20. Horn P, Münch E, Vajkoczy P, Herrmann P, Quintel M, Schilling L, *et al*. Hypertonic saline solution for control of elevated intracranial pressure in patients with exhausted response to mannitol and barbiturates. Neurol Res. 1999; 21(8):758-764. Doi: 10.1080/01616412.1999.11741010
21. Mortazavi MM, Romeo AK, Deep A, Griessenauer CJ, Shoja MM, Tubbs RS, *et al*. Hypertonic saline for treating raised intracranial pressure: Literature review with meta-analysis. J Neurosurg. 2012; 116(1):210-221. Doi: 10.3171/2011.7.JNS102142
22. Vats A, Chambliss CR, Anand KJS, Pettignano R. Is Hypertonic Saline an Effective Alternative to Mannitol in the Treatment of Elevated Intracranial Pressure in Pediatric Patients? J Intensive Care Med 1999, 14 184-188. Journal of Intensive Care Medicine. 1999; 14(4):184-188. Doi: 10.1177/088506669901400403
23. Fisher B, Thomas D, Peterson B. Hypertonic saline lowers raised intracranial pressure in children after head trauma. J Neurosurg Anesthesiol. 1992; 4(1):4-10. Doi: 10.1097/00008506-199201000-00002
24. Khanna S, Davis D, Peterson B, Fisher B, Tung H, O'Quigley J, *et al*. Use of hypertonic saline in the treatment of severe refractory posttraumatic intracranial hypertension in pediatric traumatic brain injury. Crit Care Med. 2000; 28(4):1144-1151. Doi: 10.1097/00003246-200004000-00038
25. Yildizdas D, Altunbasak S, Celik U, Herguner O. Hypertonic saline treatment in children with cerebral edema. Indian Pediatr. 2006; 43(9):771-779. PMID: 17033115