European Journal of Molecular & Clinical Medicine (EJMCM)
ISSN: 2515-8260 Volume 07, Issue 11, 2020

Original research article

A randomized clinical assessment of hypertonic saline and mannitol on intraoperative brain relaxation in patients with raised intracranial pressure undergone supratentorial tumors resection

Dr. Namrata Kumari[1], Dr. A. K. Jaiswal [2]

[1]Senior Resident, Upgraded Department of Paediatrics, Patna Medical College and Hospital, Patna, Bihar, India

[2]Professor and HOD, Upgraded Department of Paediatrics, Patna Medical College and Hospital, Patna, Bihar, India

Corresponding Author: Dr. A. K. Jaiswal

Abstract

Aim: The aim of the present study to assessment of Hypertonic Saline and Mannitol on Intraoperative Brain Relaxation in Patients with Raised Intracranial Pressure undergone Supratentorial Tumors Resection.

Methods: A prospective randomized double blind study was conducted in the Upgraded Department of Paediatrics, Patna Medical College and Hospital, Patna, Bihar, India, for 7 months. 100 patients with American Society of Anesthesiologists physical statuses I–III and aged 20–61 years with clinical or radiological evidence of raised ICP, scheduled to undergo supratentorial tumor resection were included in the study. 100 patients randomized into two equal groups. Each patient was administered 5 ml/kg of either 20% mannitol or 3% HTS over 15 minutes (min) after skin incision. Hemodynamic data, brain relaxation and serum electrolyte levels were recorded.

Results: Intraoperative brain relaxation was comparable between the two groups. There was a statistically significant difference in the mean arterial pressures (MAPs) between the two groups after one minutes (min) with a greater degree of decrease in blood pressure recorded in the mannitol group ($P = 0.037$). MAP with mannitol was significantly lower than the preinduction value after 75 min of administration of drug ($P = 0.002$). Urine output was significantly higher in the mannitol group ($P = 0.00$). Administration of HTS was associated with a transient increase in serum sodium concentrations, which was statistically significant but returned to normal within 48 h ($P < 0.001$).

Conclusions: We concluded that both mannitol and HTS provided adequate intraoperative brain relaxation. On the contrary, there was no statistically significant fall in blood pressure with HTS. Thus, we advocate the use of HTS over mannitol as it maintains better hemodynamic stability.

Key Words: Brain, elevated intracranial pressure, hypertonic saline, mannitol, relaxation

Introduction

Intracranial pressure (ICP) control has long been recognized as an important requirement for patients with severe traumatic brain injury (TBI).[1] Hypertonic solutions effectively reduce the patient's ICP without brain perfusion impairment.[2] Although mannitol has been the recommended first-line osmotic agent in this setting for years, there are concerns that its use may lead to hypotension, especially in hypovolemic patients, as well as a rebound phenomenon with increased ICP, along with renal toxicity due to increases in serum osmolality.[3,4] Thus, hypertonic saline (HS) has recently drawn attention as an alternative to

mannitol and has been found to be more effective than mannitol for reducing ICP in TBI cases.[5-7] However, hypertonic saline is also associated with potential adverse effects, such as pontine myelinolysis.[8] Moreover, few clinical studies have focused on TBI related outcomes, such as patient survival and long-term beneficial effects, and there is a lack of clarity regarding which HS is the most suitable for use in prehospital, emergency department, and intensive care unit (ICU) settings. Therefore, we aimed to assess the effects of HS versus mannitol strategies on TBI-related clinical outcomes.

Hypertonic saline (HTS) or mannitol are being routinely used to treat intracranial hypertension.[9-13] Mannitol acts through its osmotic diuretic properties that produce a reduction in brain water content and cerebrospinal fluid (CSF) pressure in approximately 20 min.[14] Besides this, it also reduces intracranial pressure (ICP) through the changes in blood fluid dynamics or blood rheology. Recently, HTS has appeared an appealing alternative to mannitol because its reflection coefficient is higher than that of mannitol (1.0 vs 0.9, respectively). Thus, HTS does not cross the intact blood–brain barrier.[15] Due to this property, HTS causes a greater increase in serum osmolality as compared to mannitol in equiomolar dosage. HTS creates a greater transendothelial osmotic gradient that results in more water movement from interstitial and intracellular brain to the intravascular space. HTS little diuretic effect and thus maintains hemodynamic stability and cerebral perfusion pressures.[16]

The present study was designed with the primary aim of comparing the effect of near equiosmolar equivolemic solutions of 3% HTS (1,024 mOsm/L) and 20% mannitol(1,098 mOsm/L) on intraoperative brain relaxation in patients with clinical or radiological evidence of raised ICP undergoing surgery for supratentorial tumors. The secondary aim was to compare the electrolyte changes after administering 3% HTS or 20% mannitol in these patients.

Material and methods

A prospective randomized double blind study was conducted in the Department of Paediatrics, Patna Medical College and Hospital, Patna, Bihar, India for 7 months, after taking the approval of the protocol review committee and institutional ethics committee.

Inclusion criteria

100 patients with American Society of Anesthesiologists physical statuses I–III and aged 20–61 years with clinical or radiological evidence of raised ICP, scheduled to undergo supratentorial tumor resection were included in the study.

Exclusion criteria

Clinical signs and symptoms of raised ICP were defined as the presence of bradycardia with hypertension, recurrent vomiting, blurring of vision, behavioral abnormalities, and excessive sleepiness or irritable behavior. Radiological signs were defined as significant midline shift (>5 mm), loss of sulci, loss of gyri, gray and white matter distinction, and significant edema surrounding the tumor. Patients with preoperative hyponatremia or hypernatremia (serum Na <135 or >145 mEq/L), intake of any hyperosmotic fluid (mannitol or HTS) in the previous 24 h, history of congestive heart failure or kidney disease and prior surgery for ventriculo-peritoneal (VP) shunt were excluded.

Patients were randomized using sealed envelopes into two groups; group M, who received 20% mannitol (osmolarity = 1,098 mOsm/l) and group HTS, who received 3% HTS (osmolarity = 1,024 mOsm/l). Patients received 5 ml/kg of either drug for intraoperative brain relaxation. Drugs were loaded in the 50 cc syringes and labeled as the test drug. Both fluids were administered over 15 min using an infusion pump after skin incision via the central line. The Anesthesiologists who recorded intraoperated data and the surgeon who assessed the

brain relaxation were blinded to the drug being given.Standard monitors were attached; non-invasive blood pressure (NiBP), electrocardiography (ECG), pulse oximetry (SpO_2), end tidal carbon dioxide concentration ($EtCO_2$), and entropy. Anesthesia was induced with propofol and fentanyl, and vecuronium was used to facilitate intubation. Invasive arterial and central venous pressures (CVPs) were also monitored. Anesthesia was maintained using propofol and fentanyl infusion titrated to keep state entropy (SE) between 40 and 60. All patients were ventilated with oxygen-nitrous oxide mixture (50%:50%) to maintain arterial partial pressure of carbon dioxide ($PaCO_2$) between 30 and 35 mm Hg.

Brain relaxation was scored by the surgeon and the anaesthetist blinded to the test drug. A four-point scale was used by the surgeon: 1 = perfectly relaxed, 2 = satisfactorily relaxed, 3 = firm brain, 4 = bulging brain.[17] A second bolus of 5 ml/kg of the study drug was given if brain was not relaxed. A three-point scale was used by the anaesthetist: = brain fully relaxed, fallen below both outer and inner tables of cranium, moving with respiration and pulsating with heartbeat, 2 = brain partially relaxed, lying between outer and inner tables of cranium, slight movement with respiration and slight pulsation with heartbeat, 3 = brain bulging out of the cranial cavity, no movement with respiration and no pulsation with heartbeat. We have used two scales to rule out the bias by the surgeon. The second scale was designed to include the brain characteristics and parameters, which are less amenable to the bias. The patients who had tight brain interfering the dura opening were managed with transient hyperventilation ($EtCO_2$ up to 25 mm Hg) with optimum airway pressures, mild hypertension, additional dosages of hyperosmolar agent (100 ml mannitol/HTS).

Hemodynamic data and $EtCO_2$ were recorded for comparisons initially at 5 min (first 15 min after induction) and then at 15 min intervals till end of surgery. Arterial blood gases and electrolytes were measured before and 1 h after giving hypertonic agents. Serum sodium and potassium were measured at 24 and 48 h also. Hourly urine output was recorded.

Statistical analysis

Considering a significant difference of 1 point in brain relaxation score between the groups to be clinically significant, a power analysis based on 95% confidence interval and with power of 90% revealed a sample size of 100 subjects (50subjects in each group). The statistical analysis was carried out using Statistical Package for Social Sciences (SPSS Inc., Chicago, IL, version 20 for Windows). The normality of the data was assessed by measures of skewness and Kolmogorov Smirnov tests of normality. The normally distributed data means were compared using t-test. For skewed data, the Mann-Whitney test was used. The Chi-square or Fisher's exact test was used to compare proportions, whichever was applicable. For time related variables, the Wilcoxon signed or paired t-test was applied. $P < 0.05$ was considered significant. Multivariate analysis of variance (ANOVA) was applied for the comparison of hemodynamic and laboratory variables between the groups.

Results

Demographic and clinical characteristics were comparable between the two groups [Table 1]. There was no statistically significant difference in heart rates between the two groups at various time intervals. There was a significant decrease in mean arterial pressure (MAP) from the preinduction value in group M after 75 min ($P < 0.05$) whereas in the HTS-group it remained stable. table . 2 compares the MAP between the two groups. Baseline CVP was comparable in both the study groups. There was a consistent rise in CVP in both the group till 1 h. But after 1 h, CVP in the HTS group remained almost the same whereas the CVP in the M group started decreasing. The difference in CVP between the two groups was statistically significant after 45 min of study [table 3]. When compared with baseline within the group, after 150 min CVP decreased significantly from baseline in the M group whereas it remained comparable to the

baseline in the HTS group. These falls in MAP and CVP in mannitol were not clinically significant and none of the patients required additional treatments for these changes other than intravenous fluid infusion.

The urine output was significantly higher in the M group as compared to the HTS group throughout the study period [Table 4]. Serum sodium was significantly higher in the HTS group but remained within normal limits [Table 4]. Difference in serum K levels was statistically significant at60 min and 24 h, but returned to baseline at 48 h [Table 4].

There was no significant difference in brain relaxation as assessed by the operating surgeon and anesthesiologist between the two groups [Table 5].

Table 1: Demographic characteristics and clinical and radiological findings

Parameters	**Group I (M) n=50**	**Group II (HTS) n=50**	**P**
Age (mean±SD) years	45.37±12.47	41.54±14.55	0.252
Sex (M/F) (n)	30/20	28/22	0.463
Weight (I/II/III) (n)	61.12±11.51	55.43±14.87	0.388
ASA status (I/II/III) (n)	41/9/0	35/15/0	0.169
Headache (P/A) (n)	35/15	35/15	1
Blurred vision (P/A) (n)	15/35	15/35	0.688
Somnolence (P/A) (n)	5/45	10/40	0.554
Papilledema (P/A) (n)	14/36	14/36	1.1
Focal neurological	38/12	35/15	0.670
deficit (P/A) (n)			
Altered consciousness (P/A) (n)	20/30	20/30	1.5
Midline shift (P/A) (n)	36/14	36/14	1.3
Obliteration of basal	24/26	10/40	0.132
cistern (P/A) (n)			
Loss of sulci (P/A) (n)	30/20	26/24	0.456
Ventricular effacement (P/A) (n)	37/13	27/23	0.216
Edema (P/A) (n)	50/0	47/3	0.336
Tumor size (P/A) (n)	126.75±127.51	78.27±86.12	0.387

Table 2.comparision of mean arterial pressure (MPV) between the groups

Parameter	**Pressure mm of hg**		**P value**
Intraoperative duration	Group M	Group HTS	
Baseline	97	97.8	
15 min	92.5	92.5	
30min	90.5	94.2	
45 min	89.4	93.9	
60min	88.1	94	
75min	85.2	95.4	0.37
90min	82.2	92.7	
105min	79.7	92.5	
120min	78.9	94.2	
135min	76	91.4	
150min	76	90.9	

165min	75.8	92.8	
180min	72.9	91.8	

Table 3.comparision of central venous pressure (CVP) between the groups

Parameter	**Pressure mm of hg**		**P value**
Intraoperative duration	Group M	Group HTS	
Baseline	5.0	6.7	
15 min	5.1	6.9	
30min	5.4	7.3	
45 min	5.6	7.4	
60min	5.0	7.5	
75min	4.5	7.3	0.002
90min	4.3	7.1	
105min	4.2	7.0	
120min	3.9	6.7	
135min	3.6	7.0	
150min	3.5	6.8	
165min	3.3	6.7	
180min	3.1	7.1	

Table 4: Urine output and electrolytes

Time	**Group M (mean±SD) n=50**	**Group HTS (mean±SD) n=50**	**P**
Urine output			
First hour	450±131.96	221.67±71.01	0.000*
Second hour	487.61±220.27	253±62.54	0.002*
Third hour	367.67±114.75	228.67±60.513	0.000*
Serum sodium			
Baseline	140.06±3.72	139.49±4.95	0.698
60 min	137.98±2.61	144.68±4.46	0.000*
24 h	138.51±3.18	142.15±3.47	0.005
48 h	136.34±2.35	139.21±2.92	0.005
Serum potassium			
Baseline	4.22±0.52	4.13±0.51	0.796
60 min	4.43±0.43	3.70±0.33	0.003*
24 h	4.12±0.37	3.71±0.32	0.020
48 h	4.29±0.45	4.7±0.37	0.555

Table 5: Brain relaxation score

Brain relaxation grade	**Group M (number/ percentage) n=50**	**Group HTS (number/ percentage) n=50**	**P**
Surgeon's assessment score			
I	15 (30%)	32 (64%)	
II	21 (42%)	9 (18%)	
III	6 (12%)	9 (18%)	
IV	8 (16%)	0	
I + II	36 (72%)	41 (82%)	0.265
Anesthesiologist's assessment score			

I	13 (26%)	31 (62%)	
II	24(48%)	10 (20%)	
III	13(26%)	9(18%)	
I + II	37 (74%)	41 (82%)	0.177

Discussion

In our study, 20% mannitol and 3% HTS produced a similar effect on brain relaxation. There are various studies in the literature reporting varied results. Two previously published crossover, randomized trials demonstrated higher efficacy of HTS in decreasing ICPs than equimolar infusion of mannitol.[18,19] The reported longer duration of ICP reduction after the use of HTS could be due to the combination of HTS with 6% hydroxyethyl starch solution[18] or with 6% dextran solution,[19] which are known to prolong the effects of HTS. Previous prospective mannitol and HTS during elective neurosurgery used different osmolar loads of the two agents and reported comparable brain relaxation between groups.[17,20]

Rozet et al.[21] compared equiosmolar, equivolemic (5 ml/kg) loads of 20% mannitol and 3% HTS in different surgical setups; supratentorial and infratentorial tumors, arteriovenous malformations, aneurysms, and subarachnoid hemorrhage. They found no difference in brain relaxation in those administered either mannitol or HTS. Here in this study, authors included a varied population and did not standardized the depth of anesthesia. Our study was conducted with similar dosages in patients with the features of raised ICP and found the similar results.

Recently, Ali et al.[22] had conducted a prospective, randomized, double-blind study in patients undergoing elective supratentorial surgeries. They compared received 5 ml/kg 20% mannitol or 3% HS as an infusion for 15 min. The authors monitored ICP using parenchymal monitor and also standardized the anesthesia by monitoring entropy. The authors concluded that 3% HS was more effective in ICP reduction than 20% mannitol during supratentorial tumor surgeries. However, the authors excluded the patients with raised ICP in their study.

In another study, Wu et al.[23] reported better brain relaxation with HTS during elective supratentorial brain tumor surgeries. The authors had used fixed volumes in their study; 160 ml of 3% HTS or 150 ml of 20% mannitol. In addition, the depth of anesthesia was not monitored in these studies, which can affect brain relaxation. We have used a weight-based dosage of 5 ml/ kg and entropy to keep the similar depth of anesthesia. This may account for the difference in results.

Dostal et al.[24] compared the infusion of 3.75 ml of equiosmolar concentrations of 3.2% HTS and 20% mannitol (osmolarity 1,099 each) and concluded that the HTS group has better brain relaxation than the mannitol group.

There was a small drop in MAP after induction in both groups. This may be due to the effect of various anesthetic agents. After 30 min, the MAP in the HTS group was maintained near baseline whereas MAP in the mannitol group was lower than baseline throughout the study period. HTS maintains MAP because of increases in cardiac output and intravascular volume.[25] HTS increases cardiac output due to its direct ionotropic effect, derived from improvement in cardiac microcirculation and contractility.[26] Volume expansion occurs because of hyperosmolarity that creates a gradient to move free water from the intracellular and interstitial compartments into the intravascular compartment. High urine output seen with mannitol might lead to the lower CVP. Compared with HTS, mannitol has a more prominent diuretic effect in all the 3 h of observation (P value <0.05). Hypernatremia after HTS was consistent with previous studies.[22,23]

Conclusion

We concluded that both mannitol and HTS are equally efficacious in reducing the intracranial hypertension. MAP and CVP are better maintained close to the baseline with HTS. Thus, we advocate the use of HTS over mannitol for reducing the ICPs in patients with features of raised ICP undergoing supratentorial tumor resection. Administration of HTS is associated with a transient increase in serum sodium concentrations that is statistically significant but clinically insignificant and returns to normal within 48 h.

Reference

1. Marmarou A, Anderson RL, Ward JD, Choi SC, Young HF, Eisenberg HM, et al. Impact of ICP instability and hypotension on outcome in patients with severe head trauma. J Neurosurg. 1991;75:S159–65.
2. Mangat HS, Wu X, Gerber LM, Schwarz JT, Fakhar M, Murthy SB, et al. Hypertonic saline is superior to mannitol for the combined effect on intracranial pressure and cerebral perfusion pressure burdens in patients with severe traumatic brain injury. Neurosurgery. 2020;86:221–30.
3. Carney N, Totten AM, O'Reilly C, Ullman JS, Hawryluk GW, Bell MJ, et al. Guidelines for the management of severe traumatic brain injury, fourth edition. Neurosurgery. 2017;80:6–15.
4. Wakai A, McCabe A, Roberts I, Schierhout G. Mannitol for acute traumatic brain injury. Cochrane Database Syst Rev. 2013;8:CD001049.
5. Oddo M, Levine JM, Frangos S, Carrera E, Maloney-Wilensky E, Pascual JL, et al. Effect of mannitol and hypertonic saline on cerebral oxygenation in patients with severe traumatic brain injury and refractory intracranial hypertension. J Neurol Neurosurg Psychiatry. 2009;80:916–20.
6. Patil H, Gupta R. A comparative study of bolus dose of hypertonic saline, mannitol, and mannitol plus glycerol combination in patients with severe traumatic brain injury. World Neurosurg. 2019;125:e221 –8.
7. Harutjunyan L, Holz C, Rieger A, Menzel M, Grond S, Soukup J. Efficiency of 7.2% hypertonic saline hydroxyethyl starch 200/0.5 versus mannitol 15% in the treatment of increased intracranial pressure in neurosurgical patients - a randomized clinical trial [ISRCTN62699180]. Crit Care. 2005;9:R530 –40.
8. White H, Cook D, Venkatesh B. The use of hypertonic saline for treating intracranial hypertension after traumatic brain injury. Anesth Analg. 2006; 102:1836 –46
9. Wisner DH, Schuster L, Quinn C. Hypertonic saline resuscitation of head injury: Effects on cerebral water content. J Trauma 1990;30:75-8.
10. Luvisotto TL, Auer RN, Sutherland GR. The effect of mannitol on experimental cerebral ischemia, revisited. Neurosurgery 1996;38:131-8.
11. PaczynskiRP, HeYY, Diringer MN, HsuCY. Multiple-dose mannitol reduces brain water content in a rat model of cortical infarction. Stroke 1997;28:1437-43.
12. 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;28:1144-51.
13. Lescot T, Degos V, Zouaoui A, Preteux F, Coriat P, Puybasset L. Opposed effects of hypertonic saline on contusions and noncontused brain tissue in patients with severe traumatic brain injury. Crit Care Med 2006;34:3029-33.
14. Jaffar JJ, Johns LM, Mullan SF. The effect of mannitol on cerebral blood flow. J Neurosurg 1986;64:754-9.

15. Rozet I, Tontisirin N, Muangman S, Vavilala MS, Souter MJ, Lee LA, et al. Effect of equiosmolar solutions of mannitol versus hypertonic saline on intraoperative brain relaxation and electrolyte balance. Anesthesiology 2007;107:697-704.
16. White H, Cook D, Venkatesh B. The use of hypertonic saline for treating intracranial hypertension after traumatic brain injury. AnesthAnalg 2006;102:1836-46.
17. Gemma M, Cozzi S, Tommasino C, Mungo M, Calvi MR, Cipriani A, et al. 7.5% hypertonic saline versus 20% mannitol during elective neurosurgical supratentorial procedures. J NeurosurgAnesthesiol 1997;9:329-34
18. Schwarz S, Georgiadis D, Aschoff A, Schwab S. Effects of hypertonic (10%) saline in patients with raised intracranial pressure after stroke. Stroke 2002;33:136-40.
19. Battison C, Andrews PJ, Graham C, Petty T. Randomized, controlled trial on the effect of a 20% mannitol solution and a 7.5% saline/6% dextran solution on increased intracranial pressure after brain injury. Crit Care Med 2005;33:196-202
20. De Vivo P, Del Gaudio A, Ciritella P, Puopolo M, Chiarotti F, Mastronardi E. Hypertonic saline solution: A safe alternative to mannitol 18% in neurosurgery. Minerva Anestesiol 2001;67:603-11.
21. Rozet I, Tontisirin N, Muangman S, Vavilala MS, Souter MJ, Lee LA, et al. Effect of equiosmolar solutions of mannitol versus hypertonic saline on intraoperative brain relaxation and electrolyte balance. Anesthesiology 2007;107:697-704.
22. Ali A, Tetik A, Sabanci PA, Altun D, Sivrikoz N, Abdullah T, et al. Comparison of 3% Hypertonic Saline and 20% Mannitol for Reducing Intracranial Pressure in Patients Undergoing Supratentorial Brain Tumor Surgery: A Randomized, Double-blind Clinical Trial. J NeurosurgAnesthesiol 2017 [Epub ahead of Print print].
23. Wu CT, Chen LC, Kuo CP, Ju DT, Borel CO, Cherng CH, et al. A comparison of 3% hypertonic saline and mannitol for brain relaxation during elective supratentorial brain tumor surgery. AnesthAnalg 2010;110:903-7.
24. Dostal P, Dostalova V, Schreiberova J, Tyll T, Habalova J, Cerny V, et al. A Comparison of Equivolume, Equiosmolar Solutions of Hypertonic Saline and Mannitol for Brain Relaxation in Patients Undergoing Elective Intracranial Tumor Surgery: A Randomized Clinical Trial. J NeurosurgAnesthesiol 2015;27:51-6.
25. Moss GS, Gould SA. Plasma expanders. An update. Am J Surg 1988;155:425-34.
26. Wildenthal K, Skelton CL, Coleman HN. Cardiac muscle mechanics in hyperosmotic solutions. Am J Physiol 1969;217:302-6.

Received: 07-09-2020 || Revised: 26-09-2020 || Accepted: 22-10-2020