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Comparison of Mannitol, Hypertonic Saline and Mannitol + Hypertonic Saline Combination for Brain Relaxation during Craniotomy

Neelesh Bhatnagar[1], Manmohan Jindal[2]

[1]Associate Professor [2]Assistant Professor, Department of Anesthesiology, Geetanjali Medical College and Hospital, Udaipur, Rajasthan 313002, India.

Abstract

Background: Hyperosmolar solutions are most commonly used to relax brain and facilitate intracranial surgery. This study was planned to compare the effects of three equiosmolar, equivolemic solutions (mannitol, 3% hypertonic saline, and mannitol+3% hypertonic saline) on intraoperative brain relaxation. *Material and Methods:* This prospective randomized study was conducted in 90 patients of age group 18-65 years with traumatic brain injury undergoing craniotomy only after approval from the institutional ethics committee. Patients were randomly allocated into three groups; Group M (received mannitol 300 ml), GROUP S (Group received 3% Hypertonic Saline 300 ml), and GROUP M+S (received mannitol 150 ml and 3% Hypertonic Saline 150 ml). Brain relaxation score was assessed by neurosurgeon on a four point scale as perfectly relaxed-1, satisfactorily relaxed-2, firm brain-3, bulging brain-4. All the patients were assessed for Glasgow coma score at 24 hrs postoperatively and at the time of discharge from the intensive care unit. *Results:* Grade 1 and Grade 2 brain relaxation scores were 4/14, 4/16 and 8/12 in Group M, Group S and Group M+S respectively. ($p>0.05$) Total urine out was 1453.33±376.68 ml in group M, 823.33±238.43 ml in group S and 1313.33±156.96 ml in group M+S respectively. ($p<0.001$) There was non-significant rise and fall of electrolyte (Na^+ and K^+) level amongst the groups. Additional rescue dose of mannitol was required in all three groups in 12, 8 and 10 patients respectively. *Conclusion:* All three hyperosmolar solutions are equally effective in providing adequate intraoperative brain relaxation during decompressive craniotomy in traumatic brain injury.

Keywords: Hyperosmolar Solutions; Brain Relaxation; Hypertonic Saline; Mannitol Traumatic Brain Injury.

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Introduction

Brain injury has been one of the commonest injuries associated with trauma and also the most devastating types of injury affecting all age patients; which is the leading cause of death worldwide [1]. Most of the traumatic brain injury (TBI) patients require large volume fluid replacement because TBI with hypotension have multi system trauma. Fluids like Ringer Lactate (RL) which are hypo-osmotic should be avoided as they can cause cerebral edema while isotonic sodium chloride can lead to hyperchloraemic metabolic acidosis [2]. Hyperosmolar solutions are most commonly used to relax brain and facilitate intracranial surgery. Mannitol has been the agent of choice for treatment of increased intracranial pressure (ICP), as being hyperosmolar, it reduces ICP by withdrawing water from the brain parenchyma to the intravascular tissue with intact blood brain barrier (BBB). It further decreases ICP by decreasing the rate of formation of CSF thus decreasing CSF volume. Most

Corresponding Author: Manmohan Jindal, Assistant Professor, Department of Anesthesiology, Geetanjali Medical College and Hospital, Udaipur, Rajasthan 313001, India.
E-mail: drmmjindal@gmail.com

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common and serious side effects of mannitol are intravascular volume depletion, hyponatremia, rebound ICP elevation and renal failure [3,4]. Hypertonic saline (HS) has been considered as an attractive alternate to mannitol for satisfactory brain relaxation and decrease in ICP [5]. Brain trauma foundation guidelines recommend HS, when mannitol fails to reduce ICP [6]. As compared to mannitol, HS also has beneficial effects like maintainance of cardiac output, mean arterial pressure and thus reduction of extravascular lung volume, leading to improved gas exchange [7]. Compared to mannitol rebound phenomenon is less common with HS administration because the co-efficient to penetrate the BBB in HS is higher than mannitol [8]. It has also been used for a long time for haemodynamic resuscitation in states of shock secondary to trauma, gastrointestinal haemorrhage, burns and sepsis [9]. HS can be used in various concentrations (1.8-30%) with varying osmolar loads and reduces ICP by creating osmotic gradient and decreasing blood viscosity leading to cerebral vasoconstriction. It has been used either alone or in combination with hyperosmotic agents [10,11]. Many studies have been conducted to compare the effect of HS and mannitol [3,12-15] but not a single study was found on literature search which has compared (mannitol+HS) equivolemic combination to HS or Mannitol. So this study was planned to compare the effects of three equiosmolar, equivolemic solutions (mannitol, 3% hypertonic saline, and mannitol+3% hypertonic saline) on intraoperative brain relaxation and postoperative outcome in traumatic brain injury.

Material and Methods

This prospective randomized study was conducted in tertiary care teaching hospital only after approval from the institutional ethics committee. Total 90 patients of age group 18-65 years with traumatic brain injury undergoing craniotomy were enrolled after taking written informed consent. Patients with electrolyte imbalance, severe cardiac, renal, respiratory diseases, traumatic brain injury with extradural hematoma, any other injury causing hemodynamic instability, large intracranial haemorrhage which itself cause massive brain bulge were excluded out. Patients were randomly allocated into three groups by computer generated random number table, according to the dose and type of hyperosmolar agent used:-

GROUP M: Group receiving mannitol 300 ml

GROUP S: Group receiving 3% Hypertonic Saline 300 ml

GROUP M+S: Group receiving mannitol 150 ml and 3% Hypertonic Saline 150 ml

All the patients were preoperatively assessed for vitals, Glasgow Coma Score (GCS), arterial blood gases including electrolytes and CT scan finding. In the operation room, standard monitoring including electrocardiogram (ECG), non-invasive blood pressure (NIBP) and pulse oximeter were attached and baseline heart rate (HR), NIBP and SPO_2 reading were recorded. Patients were preloaded with 500ml of balanced salt solution and that was used for intraoperative fluid management. After preoxygenation, general anesthesia was induced with 2mcg/kg fentanyl and 2mg/kg propofol. Muscle relaxation was achieved by 0.9mg/kg rocuronium. Intraoperatively anesthesia was maintained using oxygen-air mixture (50:50) with 50mcg-100mcg/kg/min propofol infusion. Fentanyl and vecuronium for intraoperative analgesia and muscle relaxation was used. Mechanical ventilation was adjusted to maintain $EtCO_2$ at 30+2mmHg. HR and blood pressure was kept within 20% of the baseline value. Balanced salt solution was used as a maintainence fluid at 3ml/kg/hr with additional replacement for urine output and blood loss.

At the time of scalp incision, patient received study drug as per randomization over a period of 15 min for intraoperative brain relaxation. Hemodynamic variables were recorded before induction (T_0), then regularly at an interval of 15 min for 1st hour then ½ hourly introperatively. Serum electrolytes was recorded preoperatively (T_0), after the infusion of study drug (T_i), immediately (T_c) and 24 hour (T_{24}) after the completion of surgery. Urine output was recorded hourly. Details of fluid input, blood loss and blood transfused were noted. Brain relaxation was assessed by neurosurgeon on a four point scale as perfectly relaxed-1, satisfactorily relaxed-2, firm brain-3, bulging brain-4. If the respective gradings were assessed as 3,4 (surgeon), an additional 2.5ml/kg dose of mannitol was given and hyperventilation to decrease EtCO2 to 25mmHg. At the end of surgery, patients were either extubated or shifted to neurosurgical intensive care unit for elective mechanical ventilation. All the patients were assessed for GCS at 24 hrs postoperatively and at the time of discharge from the intensive care unit (ICU). Total duration of stay in ICU was also noted.

ANOVA and paired student 't' test were used for analysis of hemodynamic and laboratory variables. Difference between the groups was analyzed using Chi-Square test. $p<0.05$ was considered significant.

Results

Demographically all the patients in each group were having similar characteristics. There was no significant difference in mean age, sex, preoperative GCS, preoperative serum electrolytes and duration of surgery among the three groups. [Table 1,2].

Total urine out was 1453.33±376.68 ml in group M, 823.33±238.43 ml in group S and 1313.33±156.96 ml in group M+S respectively. It was significantly less in group S. (p<0.001) Total blood loss was significantly more in group S (746.67±348.13 ml) as compared to group M (576.67±238.43 ml) and group M+S (563.33±171.92 ml). (p<0.05).

There was no significant difference in patients with grade 1 and grade 2 (which was acceptable to neurosurgeon) brain relaxation. These scores were 4/14, 4/16 and 8/12 in Group M, Group S and Group M+S respectively. (p>0.05). Additional rescue dose of mannitol was required in all three groups in 12, 8 and 10 patients respectively [Table 1].

There was slight rise in serum sodium levels in both the groups S and M+S after the infusion of study drug though this increase in serum sodium levels were statistically not significant (p>0.05). This rise was transient which returned near baseline values on completion of surgery in both the groups. In group M, there was slight non-significant decrease in sodium levels immediately after the infusion of study drugs which persisted upto 24 hours postoperatively [Figure 1].

Potassium levels decreased after the infusion of study drug in groups M and M+S, though this decrease was not statistically significant (p>0.05). However there was a slight rise in potassium levels in group S but this rise was also not statistically significant [Figure 2].

The mean length of stay in the ICU in groups M, S, M+S was 5.73±2.18, 5.46±1.89 and 5.00±2.10 days respectively (p>0.05). In present study, mortality was not found in any group during ICU stay. There was no difference in the mean baseline GCS, mean GCS at 24 hours postoperatively and mean GCS at the time of discharge from the ICU among the three groups. Mean GCS score was significantly improved in group S from preoperative 9.53±3.15 to 11.13±2.03 at the time of discharge. (p<0.05) [Table 2].

Table 1: Comparison of demographic data, surgery data, anaesthesia data and brain relaxation score in all the three groups

	Group M (n=30)	Group S (n=30)	Group M+S (n=30)	P value
Age (yrs) (Mean ±SD)	35.27±9.76	35.53±9.13	36±5.91	0.05
Sex (M/F ratio)	28/2	28/2	26/4	0.05
Duration of Surgery(min) (Mean ±SD)	150±20.59	145±21.09	153.33±20.05	0.05
Total Urine output(ml) Mean ±SD	1453.33±376.68	823.33±238.43	1313.33±156.96	**0.001***
Total Fluid intake (ml) Mean ±SD	2530±419.28	2440±232.08	2612.67±257.38	0.05
Total Blood Loss (ml) Mean ±SD	576.67±238.43	746.67±348.13	563.33±171.92	**0.05***
Rescue dose of mannitol required (number of patients)	12	8	10	0.05
Brain relaxation (number of patients) excellent/satisfactory/firm/bulging	4/14/10/2	4/16/6/4	8/12/6/4	0.05
ICU Stay (Days) Mean ±SD	5.73±2.18	5.46±1.89	5.00±2.10	0.05

*significant

Table 2: Comparison of preoperative GCS, after 24 hr, at discharge

	GCS score			P value
	Pre-operative	After 24 hr	At discharge	
Group M (n=30)	9.8±3.41	9.87±3.19	10.60±3.08	0.05
Group S (n=30)	9.53±3.15	9.53±2.50	11.13±2.03	**0.05***
Group M+S (n=30)	10.07±2.24	10.27±1.98	11.27±1.91	0.05

*significant

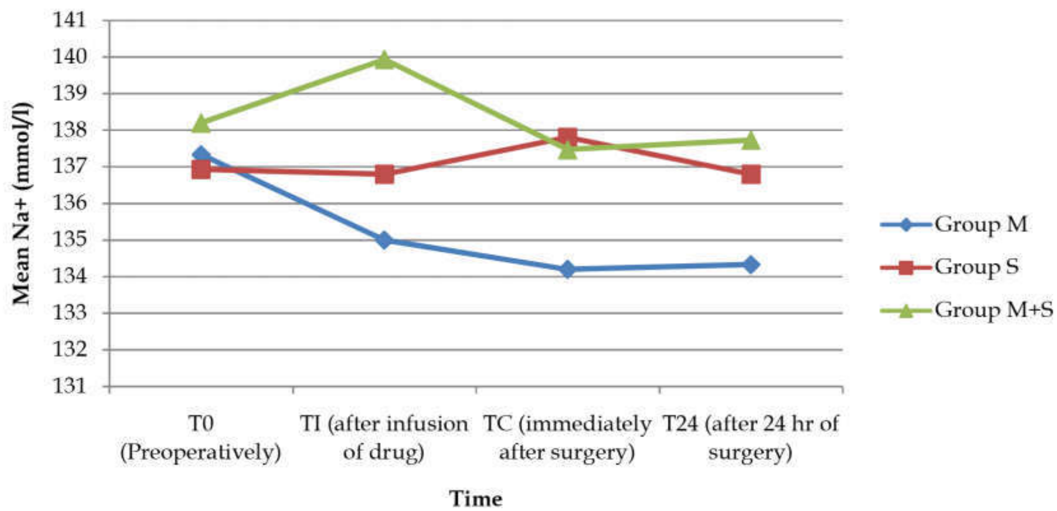

Fig. 1: Mean Na+ level in all the three groups

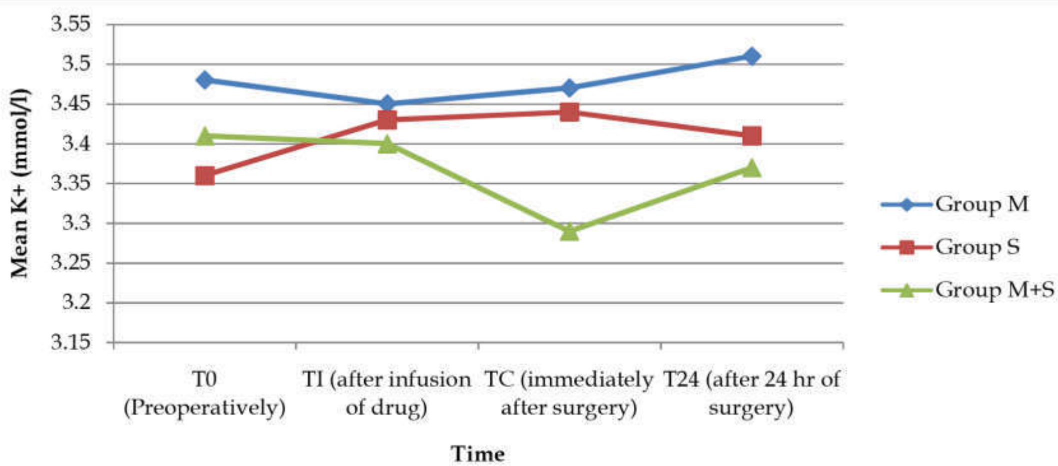

Fig. 2: Mean K+ level in all the three groups

Discussion

Mannitol has been used since long for brain relaxation as a standard hyperosmotic agent.[16] Equiosmolar dose of both mannitol and hypertonic saline were found effective in providing brain relaxation in many studies. Osmotic gradient induced shift of extravascular to intravascular water across the blood brain barrier is the main mechanism of action of both the solutions [17]. Mannitol has more prominent effect on urine output as diuretic action and hypertonic saline has more action on electrolyte. In view of that present study has compared combination of equiosmolar and equivolumic solutions (mannitol + HS) with either of that for brain relaxation.

In present study there was no significance difference between all the groups for intraoperative brain relaxation. These results were similar to other studies which have also compared equiosmolar and equivolemic solutions 20% mannitol versus 3% HS for intraoperative brain relaxation during aneurysm surgery and found no significant difference in brain relaxation between both the groups [3,12]. Various other studies have reported hypertonic saline group more effective than mannitol group [13-15]. This difference could be due that these studies had used non-equiosmolar and unequal volume of hyperosmotic solutions.

Numbers of patients requiring rescue doses of mannitol were similar in all the groups. Other studies have also found similar results with no significance difference of rescue dose of mannitol [3,12]. This could be due to equiosmolar concentrations of hyperosmolar solutions.

Mannitol has been reported hypokalemia and HS has reported hypernatremia in various studies [3,12].

But present study found non-significant rise and fall of electrolyte (Na+ and K+) level amongst the groups. Total urine out was found significantly more in mannitol group. This could be due to the more diuretic action of mannitol as compared to hypertonic saline [17].

There was no death in present study in any of the group and difference between duration of ICU stay was also non-significant amongst all the groups. Mean GCS was improved from the base line value in all the three groups but it was significantly improved in group S only at the time of discharge. Wu et al also found non-significant difference in duration of ICU stay among the groups [13]. This could be due that HS causes more decrease in intracranial pressure and with more hemodynamic stability which improve brain swelling and cerebral perfusion and attenuate the progression of secondary brain injury [18]. This is the first type of randomized study which has compared the effect of equiosmolar and equivolemic solutions of HS, mannitol and mannitol+HS on intraoperative brain relaxation.

Conclusion

The present study concludes that all the three hyperosmolar solutions are equally effective in providing adequate intraoperative brain relaxation during decompressive craniotomy in traumatic brain injury because there was no significant difference when equivolemic and equiosmolar solution of either mannitol or HS or when used in combination.

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