ORIGINAL RESEARCH

Effect of 3% hypertonic saline and 20% mannitol on intraoperative brain relaxation during decompressive craniectomy surgery following traumatic brain injury

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ABSTRACT

Aim: The aim of the study was to compare the effect of mannitol and hypertonic saline on intraoperative brain relaxation during decompressive craniectomy in traumatic brain injury. **Methods:** A total of 100 patients ,scheduled to undergo craniectomy were enrolled in this study and were divided into two groups of 50 each. Group M patients received 5 ml/kg 20% mannitol(M) and Group HTS received 3% hypertonic saline (HTS) at the start of scalp incision. Hemodynamics, fluid balance and serum electrolytes, were measured at 0, 15, 30, and 60 min and 6 h after infusion. Intensive Care Unit stay and requirement of ventilation was also recorded. The surgeon assessed brain relaxation on a four-point scale (1 = Relaxed, 2 = Satisfactory, 3 = Firm, 4 = Bulging). $P < 0.05$ was considered significant. **Results:** Intraoperative brain relaxation in the HTS group (relaxed /satisfactory /firm/ bulging,n=28/17/4/1) were better than those observed in the M group (relaxed/satisfactory/firm/bulging(n = 20/18/8/4). The levels of serum sodium were higher in the HTS group compared to group M. **Conclusion:** We concluded that HTS provided better brain relaxation than mannitol during decompressive craniectomy in traumatic brain injury, without affecting ICU and hospital stay.

Key words: hypertonic saline, mannitol, intraoperative, brain relaxation

INTRODUCTION

Providing brain relaxation during neurosurgical procedures, which allows retraction of the brain with a reduction of consequent retractor ischemia is one of the important anesthetic goals. Osmo therapy with hyperosmotic agents such as mannitol and hypertonic saline (HTS) administered before opening the duramater, is widely used to produce cerebral relaxation and facilitate intracranial surgery. [1] Osmolality is the primary determinant of water movement through the intact blood brain barrier (BBB), and it is predictable. If we increase serum osmolality, normal brain tissue would dehydrate, and the cerebral volume, as well as the intracranial pressure (ICP), would be reduced.[2] Hyperosmolar solutions like mannitol(M) and hypertonic saline (HTS) have both been used for treatment of raised intracranial pressure. The hyperosmolarity of mannitol and HTS, combined with the impermeability of the blood brain barrier (BBB) to mannitol and sodium, provides favourable conditions to move water from the brain to the intravascular compartment. However, the differential effects of these agents on clinical conditions in patients undergoing neurosurgery have not been compare.[3] Mannitol is considered as the standard and is recommended as a first choice hyperosmotic agent for treatment of increased intracranial pressure in North America and Europe.[4] However, a number of prospective clinical trials comparing the effects of mannitol and HTS on intracranial pressure have suggested that HTS is at least as effective as, if not better than, mannitol in the treatment of intracranial hypertension.[5] Mannitol has become the traditional basis of hyperosmolar therapy.

However, it can be associated with severe adverse effects such as intravascular volume depletion, rebound ICP elevation, and renal failure. Hypertonic saline solutions (HTS)have gained renewed interest as an alternate therapy and recently have been used in neurosurgical patients.[6] Several clinical studies comparing the effects of mannitol and HTS on ICP have suggested that HTS is as effective as mannitol if not better for treating intracranial hypertension.[7] The present study was conducted to compare the effects of an equiosmolar bolus of HTS with mannitol on intraoperative brain relaxation in patients undergoing elective craniotomy.

METHODS

Written informed consent was taken from a legally authorized representative of patients before involvement in this study.100 adult patients aged 18–65 years, with traumatic brain injury undergoing craniectomy were enrolled into this prospective, randomized, double-blinded study from April 2021 to April 2022 in a tertiary care hospital. Patients scheduled to undergo craniectomy were included. Exclusion criteria were age younger than 18 yr, preoperative hyponatremia or hypernatremia (serum Na <130 or >150 mEq/l), treatment with any hyperosmotic fluid (mannitol or HTS) in the previous 24 h, or history of congestive heart failure or kidney disease. After randomization using sealed envelopes, patients were assigned to receive 5 ml/kg of 20% mannitol (M group) or 3% HTS (HTS group) for intraoperative brain relaxation. Both fluids were administered over 15 min using an infusion pump with the type of fluid blinded to both surgeon and anesthesiologist. General anesthesia was administered to all patients by the anesthesiologist. Mechanical ventilation was adjusted to maintain partial pressure of carbon dioxide ($Pa_{CO}2$) between 35 and 40 mmHg. Fluids were given intravenously to maintain CVP at 8 mmHg or greater. After skin incision, the study drug (mannitol or HTS) was administered via the central line.Brain relaxation was scored by the surgeon upon opening the dura on a four-point scale: 1 = perfectly relaxed, 2 = satisfactorily relaxed, 3 = firm brain, 4 = bulging brain.[8] If the surgeon was not satisfied with the degree of brain relaxation on dural opening, a second bolus of 5 ml/kg of the study drug was given, and hyperventilation was initiated to provide relaxation for surgical access. Following variables were measured: Hemodynamic parameters including arterial blood pressure (systolic and diastolic) and CVP, perioperative fluid balance,urine output, arterial blood gases, and electrolytes. All the variables were measured and recorded before infusion (T0) and after administration of study drug at15 min (T15), 30 min (T30), 60 min (T60) and hourly up to 6 h (T360) after infusion. Urine output was recorded every hour. All the patients were extubated at the end of surgical procedure and transferred to Intensive Care Unit (ICU) for postoperative care. For power analysis calculation, we considered a difference of 1 point in brain relaxation score between the groups to be clinically significant. A power analysis based on 95% confidence interval with 90% power, the sample size of 25 in each group was sufficient. Data were entered in MS Excel software and analyzed using SPSS software version 21.0, IBM Inc. Frequency and proportion data (demographic/categorical) were analyzed using Chi-square/Fisher exact test. Continuous data were analyzed using ANOVA and student *t*-test (unpaired). For non-normal distribution, non-parametric tests such as the Kruskal-Wallis test and Mann–Whitney U test was used. Results on continuous measurements are presented as Mean ± SD. $P < 0.05$ was considered significant.

RESULTS

The difference in age, weight, severity of illness, and sex between two groups was comparable [Table 1].

Table 1: Demographic data of the groups

Variables	Group HTS (*n*=50)	Group M(*n*=50)	P Value
Age (years)	44.39±12.36	45.17±12.47	0.324
Male/female	40/10	42/08	0.125
Weight (Kg)	70.61±6.2	69.52±6.4	0.214
ASA status II/III	45/5	43/7	0.364
GCS <8	12	14	0.372
8-12	15	18	0.245
>12	23	18	0.173

The hemodynamics, PaCO2, and CVP levels were not significantly different between the two groups. In our study, the number of patients with different brain relaxation scores, were adequately relaxed (28), satisfactorily relaxed (17), firm (4) and bulging (1) in group HTS and (20), (18), (8), and (4) in group M respectively which shows that HTS provided better brain relaxation than mannitol [Table 2].

Table 2: Brain relaxation scores between two groups

Brain relaxation score	Group HTS (*n*=50)	Group M (*n*=50)	P Value
Relaxed	28	20	0.014
Satisfactory	17	18	0.568

Firm	4	8	0.195
Bulging	1	4	0.035

Table 3: Surgical and anaesthetic data

Variables	Group HTS(*n*=50)	Group M(*n*=50)	P Value
Fluid input (L)	7.234±0.46	7.658±0.79	0.384
Amount of drug administered (ml)	389.85±20.34	435.55±18.12	0.345
Urine output (L)	4.87±0.35	5.97±0.18	0.019
ICU stay (days)	1.98±1.14	1.64±1.78	0.176
Number of patients required additional dose of the drug	8	18	0.012
Operation time (min)	287.45±28.22	283.76±25.84	0.319
Number of patients required additional hyperventilation	9	12	0.345
Hospital stay (days)	9	10	0.469

18 patients in group M required additional dose of the drug as compared to 8 patients in group HTS, which was found statistically significant. It was observed in our study that group HTS was associated with significantly higher levels of serum sodium compared to group M.

The difference between fluid input at different time intervals in two groups was statistically insignificant ($P > 0.05$).Urine output after 6 h in the group HTS and group M was statistically significant.[Table 3].

DISCUSSION

We studied effects of equiosmolar boluses of HTS and mannitol on the clinical brain condition in patients under going decompressive craniectomy procedures. The major findings of our study are that HTS provided better brain relaxation compared with mannitol. Mannitol has a more prominent diuretic effect, which is associated with a less positive fluid balance and increasing lactemia over time.[8]Previously, the effect of mannitol and HTS on the brain in patients without increased intracranial pressure has been investigated in two studies in patients undergoing elective craniotomies for various neurosurgical procedures.[8] De Vivo et al.[9] compared three different regimens and combinations of mannitol and HTS: (1) 0.5-g/kg bolus of mannitol (n = 10) versus(2) 0.25-g/kg bolus of mannitol followed by continuous infusion of 3% HTS (n = 10) versus (3) bolus of 3% HS followed by continuous infusion of 2% and 1% HTS (n = 10). Using the scale of brain relaxation similar to ours, the authors did not find any difference between the groups.[9] In our study, all patients without SAH had satisfactory brain relaxation after the bolus of hyperosmotic fluid, whereas 60% of patients with extensive SAH in both groups did not have adequate brain relaxation necessitating a second bolus of hyperosmotic fluid and hyperventilation. We also maintained $Pa_{CO}2$ between 35and 40 mmHg to avoid an influence of carbon dioxide on the brain bulk, until it was assessed by the surgeon. Then, if needed, hyperventilation was initiated by the attending anesthesiologist's choice. Physiologic effects of hyperosmotic fluids on the brain have been compared in multiple animal and human studies with various brain pathologies, including SAH. The principal mechanism of action of both mannitol and HTS solutions is the creation of an osmolar gradient across the BBB due to impermeability of the BBB to mannitol and Na. Therefore, an intact BBB is required for intravascular water absorption. Indeed, a decrease in intracranial pressure with increased serum osmolality, and decreased brain water content with hyperosmotic treatment in healthy, but not injured, brain tissue has been shown in animals. In humans, a correlation between an increased concentration in serum sodium and osmolality and a decrease in intracranial pressure and brain water content in noninjured brain areas has been shown in patients with traumatic brain injury and brain tumors, treated with either HTS or mannitol. In this regard, our data showing equally effective brain bulk reduction with HTS and mannitol in patients without SAH is consistent with the classic theory of hyperosmotic therapy.[10] The effectiveness of the hyperosmolar solute depends on its "reflection coefficient" determining the relative impermeability of the BBB to the solute, where 1 means an absolutely impermeable solute and 0 means an ideally permeable solute. Because the reflection coefficient of sodium is 1 and that of mannitol is 0.9, HTS may have potential advantages over mannitol.[11] There are some data in animal and human studies suggesting HTS is more effective than mannitol in reducing an increased intra-cranial pressure, but unfortunately, differences in the osmolar load between solutions, as well as differences in study design, did not allow definitive conclusions.[12] In our study, the equiosmolar load of mannitol and HTS led to similar acute increases in serum osmolality by the end of infusion, which is consistent with the data of Erard et al.,[13] who compared an equiosmolar load but different volumes of 7.5% HS and 20% mannitol. With both agents, we observed a sustained increase in blood osmolality for 6 h, and an increase in CSF osmolality 6 h after the treatment. Because the composition of CSF is highly dependent on the integrity of the BBB, an observed increase of osmolality in CSF with both agents and an increase of

Na in CSF with HTS may reflect an impaired permeability of the BBB. On the other hand, it may suggest dynamics of mannitol and sodium over time across the BBB. Recently, Ito et al.[14] reported an increase in CSF sodium over time after a single bolus of HS in dogs with an intact BBB. With an impaired BBB, aggravation of cerebral edema with HTS has been reported, suggesting a potentially detrimental effect of HS due to leakage of sodium through the BBB. With regard to mannitol, an increase in CSF osmolality had been reported to correlate with the dose of mannitol after repeated treatments. Along with the hyperosmotic mechanism, an improved blood rheol- ogy with the shrinkage of erythrocytes, and a decrease in CSF production, antiinflammatory and other prop- erties of both mannitol and HS are believed to play a role in their therapeutic action on healthy as well as injured brain.[15]The patients in our study remained hemodynamically stable, without significant changes in mean arterial pres- sure with both mannitol and HS infusions. Despite the similarities in hemodynamic response in the groups, the use of mannitol did result in a more profound diuretic effect and a less positive fluid balance, and this was associated with an increase in blood lactate over time, whereas no changes in blood lactate were observed with HS. The negative fluid balance with man- nitol suggests that the increase in lactate may be secondary to relative hypovolemia. On the other hand, our finding of high baseline lactate in CSF in patients with SAH hemorrhage is a well-known phenomenon,[16] and the clinical relevance of relative blood hyperlactemia and CSF hyperlactemia in patients with SAH remains unknown, because brain metabolism of oxygen and lactate stayed within normal limits and did not differ between the groups. Hypertonic saline caused an increase in blood sodium, which was sustained for 6 h, and acute, but transient, hypokalemia. In contrast, mannitol caused an acute hyponatremia, but a stepwise increase of potassium over time. Different changes of potassium such as hypokalemia and hyperkalemia have been previously reported with mannitol.Hyperkalemia after mannitol administration has been reported,[17] but the exact mechanism of this phenomenon is unknown. One of the suggestions includes a cellular potassium efflux with the water, as a result of hyperosmolar condition. The development of hypokalemia with HTS can be explained as a compensatory mechanism to maintain electrical neutrality in circumstances of induced hyperchloremic acidosis associated with the infusion.[18]Although the study groups were well matched for most characteristics, we did not match various tumor related factors such as the tumor size, histology, perifocal edema, and midline shift, which could independently affect the brain relaxation. The study did exclude patients with Glasgow Coma Scale score <13 and patients with signs of increased ICP, but it is still possible to have patients without signs of increased ICP but with variable intracranial compliance. TBI can result in permanent neurological deficits leading to increased hospital stay and morbidity.[19] Chang et al.[20]had compared the effect of equiosmolar doses of 3% HS and 20% mannitol after decompressive craniectomy and found no significant difference in mean ICU and hospital stay, ICP burden (h of raised ICP/day), GCS score at discharge, and mortality. In our study, we found a similar length of stay in all three groups. There was a significant improvement in GCS of severe head injury patients at 24 h and discharge from ICU in group HTS which could be attributed to the higher osmolar load.

CONCLUSION

We concluded that 3% HTS provided better intraoperative brain relaxation than mannitol during decompressive craniectomy.

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