ORIGINAL ARTICLE

Mannitol versus hypertonic saline for intra-operative brain relaxation during aneurysm surgery

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Abstract

Background: The study was designed to compare the effects of equiosmolar and equivolemic 3% hypertonic saline (HTS) and 20% mannitol (M) on brain relaxation during aneurysm surgery. **Materials and Methods:** A prospective, randomised, double-blind study was undertaken in patients scheduled for surgical clipping of intracranial aneurysms presenting with Fisher grade I, II or III. The patients received either 300 mL of 3% hypertonic saline (HTS group) or 300 mL of 20% mannitol infusion (M group) during a period of 15 minutes at the start of scalp incision. The $PaCO_2$ was maintained at 3.4-4.7 kilo Pascal, arterial blood pressure was maintained within ± 20% of baseline and central venous pressure was maintained at 5-10 cm of water. The haemodynamics, arterial blood gases and serum sodium concentration were compared. Surgeons assessed the condition of the brain as bulging, firm, satisfactorily relaxed and perfectly relaxed. An anaesthesiologist also assessed intra-operative brain relaxation. **Results:** The brain relaxation achieved with hypertonic saline was as good as that with mannitol. Urine output with mannitol was higher than with hypertonic saline ($P < 0.04$). Hypertonic saline caused an increase in serum sodium over one hour ($P < 0.001$) but resolved in 24 hours. **Conclusions:** The brain relaxation was equal in both the groups as assessed by the anaesthesiologist as well as the surgeon while the transient rise in serum sodium in hypertonic saline group returned to normal within 24 hours.

Key words: Aneurysm surgery, hypertonic saline, mannitol

INTRODUCTION

Hyperosmolar solutions are used widely to relax the brain and facilitate exposure and reduce retractor pressure.[1] A number of prospective clinical trials comparing the effects of mannitol and Hypertonic saline (HTS) on intracranial pressure have suggested that HTS is as effective as, if not better than mannitol, in the treatment of intracranial hypertension.[2-4] Studies showed beneficial effects of continuous HTS infusion on intracranial pressure in paediatric traumatic brain injury patients.[5,6]

Access this article online	
Quick Response Code:	Website: www.jnaccjournal.org
	DOI: 10.4103/2348-0548.148382

Two prospective studies comparing mannitol and HTS in patients undergoing elective neurosurgery reported similar brain conditions among groups.[7,8] However, these studies did not address the comparative efficacy between HTS and mannitol as the study design did not control for equiosmolar concentrations of the two solutions. In one study where equiosmolar and equivolemic loads of mannitol and hypertonic saline were compared, patients posted for supratentorial tumour surgeries were included.[9] While in the other study, patients posted for all types of surgeries (supratentorial tumours, infratentorial tumours, arteriovenous malformations and aneurysms) were included.[10]

The current study was designed to compare the effect of equiosmolar equivolemic solutions of mannitol (M) and hypertonic saline (HTS) on intraoperative brain relaxation as the primary endpoint of the study, and electrolyte changes as secondary endpoints, in patients undergoing craniotomy for aneurysm surgery.

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MATERIALS AND METHODS

After the approval of hospital ethics committee and written informed consent, 31 adult patients were enrolled into a prospective, randomised, double-blinded study. American society of Anesthesiologists (ASA) physical status I to III patients scheduled to undergo craniotomy for aneurysm surgeries presenting in Fisher grade[11] I, II or III were included. Patients with age < 18 yr, ASA physical status IV and V, preoperative hyponatremia or hypernatremia (serum Na < 135 or > 150 mmol/l), who had received treatment with any hyperosmotic fluid (mannitol or HTS) in the previous 24 hr or with history of congestive heart failure or kidney disease were excluded from the study.

Randomisation was achieved by computer generated random number table. Random group assigned was enclosed in a sealed opaque envelope to ensure concealment of allocation sequence. After shifting the patient inside operation theatre, sealed envelope was opened by anaesthesiologist not involved in the study to prepare the drug solution for infusion according to randomisation. The observer who collected the intra-operative data as well as the operating surgeon was blinded to the drug solution administered.

Patients were assigned to receive 5 ml/kg of either 20% mannitol (1 g/kg, osmolarity = 1,098 mOsm/l; mannitol group) or 3% Hypertonic saline (osmolarity = 1,024 mOsm/l; HTS group) according to randomisation for intra-operative brain relaxation. The study drug was administered through the central line over 15 min using an infusion pump after skin incision.

General anaesthesia was induced with propofol or sodium thiopental, along with opioids and muscle relaxant as determined by the attending anaesthesiologist. Anaesthesia was maintained with inhalational agents (1-1.2% minimum alveolar concentration of isoflurane or sevoflurane) in oxygen–nitrous oxide mixture, and muscle relaxants as decided by the attending anaesthesiologist. Mechanical ventilation was adjusted to maintain partial pressure of carbon dioxide ($PaCO_2$) between 3.4 and 4.7 kiloPascal.

Measured variables included (1) haemodynamic variables, including mean arterial pressure and CVP; (2) laboratory data, including blood gases and electrolytes measured in arterial blood. All variables were measured and recorded before infusion (T0) and after administration of the study drug at 15 min (T15), 30 min (T30), 60 min (T60), 2 h (T120), 3 h (T180), 24 h and 48 h after infusion. Urine output was recorded every hour.

Brain relaxation was assessed by the surgeon upon opening the dura on a four-point scale[12]: 1 = perfectly relaxed, 2 = satisfactorily relaxed, 3 = firm brain, 4 = bulging brain. 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. Brain relaxation was also be assessed by an anaesthesiologist unaware of the agent administered on a three point scale: 1 = Brain fully relaxed (below both outer and inner tables of cranium moving with respiration and pulsating with heart beat), 2 = Brain partially relaxed (lying between outer and inner tables of cranium, slight movement with respiration and slight pulsation with heart beat), 3 = Brain bulging out of cranial cavity, no movement with respiration and no pulsation with heart beat.

Statistical analysis

A change in one point in brain relaxation of surgeon's score was considered to be clinically significant. A power analysis based on 95% confidence interval and β-error of 5% revealed a sample size of 24 subjects (12 subjects in each treatment group). ANOVA and paired Student '*t*' test were used for analysis of hemodynamic and laboratory variables. Differences in categorical variables in patient characteristics and brain relaxation between the mannitol and HTS groups were analysed using Chi-square. A $P < 0.05$ was considered significant.

RESULTS

Thirty-one adult patients divided into HTS group and M group were studied over a period of 1 year. There was no significant difference in age, weight, ASA status and Fisher grade between the groups with the above characteristics normally distributed in our sample [Table 1]. Heart rate, mean arterial pressure, end-tidal carbon dioxide and central venous pressure (CVP) were comparable between the groups.

There was no significant difference in brain relaxation assessed by operating surgeon between both the groups [Table 2]. Grade I and grade II relaxation was considered to be acceptable. Fourteen out of 16 patients had acceptable relaxation in HTS group while 12 out of 15 patients had similar relaxation score in M group ($P = 0.57$).

Table 1: Demographic characteristics

	Group HTS *N*=16	Group M *N*=15
Age (mean±SD) year	45.25±11.67	48±15.03
Sex (M/F) (*n*)	7/9	6/9
Weight (mean±SD) (kg)	60.18±3.65	60.53±2.82
ASA status (*n*)	8/7/1	7/4/4
Fisher grade (*n*)	1/7/8	2/4/9

The values are mean±SD or *n*, SD = Standard deviation, M/F = Male/Female, Kg = Kilogram, *n* = Number, HTS = Hypertonic saline

Similar to the surgeon's assessment, no significant difference in brain relaxation was found when assessed by anaesthesiologist blinded to the drug administered [Table 3]. Fifteen out of 16 patients had acceptable relaxation (grade I or II) in HTS group while 13 out of 15 patients had similar relaxation score in M group ($P = 0.57$).

Group M had a significantly higher urine output in the first hour than group HTS ($P = 0.04$). In the second and third hour also, group M had a higher mean urine output though the difference was not significant statistically [Figure 1]. Baseline serum sodium levels were comparable in both the study groups. There was significant rise in serum sodium concentration in HTS group during first hour of drug administration which was found to be statistically significant ($P < 0.001$) as compared to M group. At 24 and 48 hours, serum sodium was similar in both the groups [Figure 2].

Table 2: Brain relaxation as graded by surgeon

Relaxation	Group HTS *N*=16 (%)	Group M *N*=15 (%)	*P*
I	6 (37.5)	7 (46.7)	0.67
II	8 (50)	5 (33.3)	0.34
III	2 (12.5)	2 (13.3)	1
IV	0	1 (6.7)	0.48
I+II	14 (87.5)	12 (80)	0.57

The values are (*n*)-number of patients or (%) - percent of total, HTS = Hypertonic saline

Table 3: Brain relaxation as graded by anaesthesiologist

Relaxation	Group HTS *N*=16 (%)	Group M *N*=15 (%)	*P*
I	11 (68.8)	9 (60)	0.71
II	4 (25)	4 (26.7)	1
III	1 (6.3)	2 (13.4)	1
I+II	15 (93.8)	13 (86.7)	0.57

The values are (*n*) – number of patients or (%) – percent of total, *n* = Number, HTS = Hypertonic saline

DISCUSSION

The study was unique in that it was conducted exclusively in aneurysm surgery which has not been reported in the literature. Patients included in the study had aneurysmal grades - I, II or III (Fisher's[11]). Thus patients with overt intracranial hypertension were excluded.

In previous studies,[9,10] only surgeon's scale[12] was employed to assess the brain relaxation. We utilised anaesthesiologist's scale used conventionally to judge brain relaxation in our centre in addition to the surgeon's scale. This addition was important since a single anaesthesiologist blinded to the study drug commented on the brain relaxation which minimised observer bias.

Since grade I and II relaxation was found to be acceptable for surgical manoeuvering, grade I and grade II were combined. The findings suggested that the brain relaxation achieved by hypertonic saline is similar to that achieved with mannitol and showed that anaesthesiologist's assessment of brain relaxation was comparable to the surgeon's assessment in the surgical field.

While using both these drugs, it was important to use equiosmolar and equivolemic loads. This is due to the fact that these drugs act by virtue of their osmotic properties. The principal mechanism underlying these effects is the induction of a water shift from brain tissues to the intravascular space on account of hyperosmolarity of hypertonic saline or mannitol, provided the blood brain barrier (BBB) is impermeable to hypertonic saline

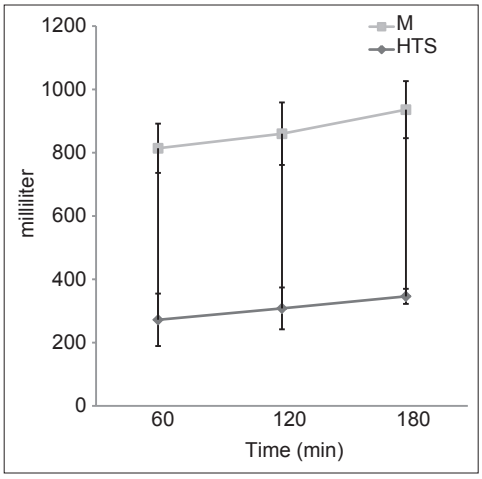

Figure 1: Changes in urine output over time

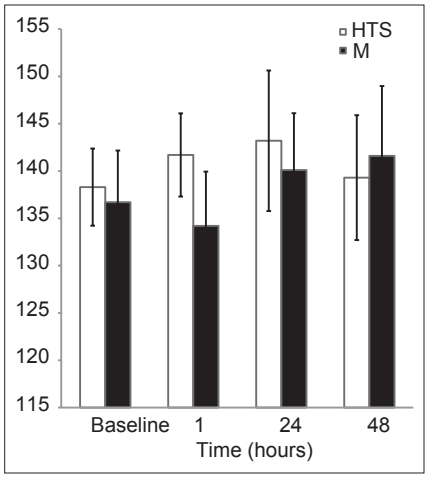

Figure 2: Changes in sodium levels over time

and mannitol. This shift of water reduces the bulk of brain. Gemma *et al*.[7] administered equal volumes of 7.5% HTS and 20% mannitol to the patients undergoing elective neurosurgical procedures and found satisfactory brain relaxation in all cases. De Vivo *et al*.[8] compared three different regimens and combinations of mannitol and HTS for brain relaxation in elective craniotomies in patients with supratentorial tumours and found no difference in brain relaxation. Wu *et al*.[9] compared 3% hypertonic saline and mannitol for brain relaxation during elective supratentorial brain tumor surgery and found better brain relaxation in the HTS group. Rozet *et al*.,[10] compared the effects of equi-osmolar solutions of mannitol and hypertonic saline on brain relaxation and electrolyte balance in different surgeries and found no difference in brain relaxation between the two groups.

There was increase in urine output on administration of mannitol throughout the study period which was statistically significant during the first hour only ($P = 0.04$). This increase was expected as mannitol is an osmotic diuretic. Our findings are consistent with previous studies.[9,10] Increase in urine output was also evident in HTS group which was not significant statistically. It may be due to natriuresis[13] (elevated renal perfusion pressure, increased glomerular filtration rate and decreased sodium absorption). Response is mediated through humoral activity in brain and heart. This is beneficial in the patients of traumatic brain injury as diuresis may result in hypovolemia which is detrimental. Hence administering HTS is being considered more frequently in such patients.[14-20]

Present study showed transient and statistically significant increase in serum sodium 1hour following administration HTS which normalised within 24 hours. No change was observed in the mannitol group. Hypernatremia after HTS was consistent with previous studies.[9,10] According to Moss *et al*.,[21] a 250-mL bolus of 7.5% NaCl elevates serum sodium to 160 mmol/L. Shackford *et al*.[22] described that serum sodium and osmolarity changes resolve rapidly because of reduction in free water renal clearance, particularly if judicious administration of free water is allowed. Follow-up till 48 hours has not been done in the previous studies.

Regarding potassium, statistically significant rise has been found in the M group in the present study at 24 hours. Hyperkalemia after mannitol administration has been reported[23] which may be due to cellular potassium efflux with the water, as a result of hyperosmolar condition.[24]

Limitations

We did not monitor the brain function i.e., brain tissue oxygen tension, cerebral blood flow, and intracranial pressure and cerebral blood flow velocity in our study. Further, the follow-up was done upto 48 hours only.

CONCLUSION

To the best of our knowledge, this is the only prospective, double-blind, randomised human study performed to date that demonstrates the differential effects of HTS and mannitol on intra-operative brain relaxation in aneurysm surgery. The data obtained allows us to conclude that 3% HTS provided similar brain relaxation compared with 20% mannitol during aneurysm surgery.

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How to cite this article: Sharma S, Grover VK, Mathew PJ. Mannitol versus hypertonic saline for intra-operative brain relaxation during aneurysm surgery. J Neuroanaesthesiol Crit Care 2015;2:23-7.

Source of Support: Nil, **Conflict of Interest:** None declared.