A COMPARISON OF 3% HYPERTONIC SALINE AND MANNITOL FOR BRAIN RELAXATION DURING ELECTIVE SUPRATENTORIAL BRAIN TUMOUR SURGERY

Medical Science

Dr. Arabinda Mazumdar

Assistant Professor, Dept of anesthesiology, College of medicine & JNM hospital.

Dr. Ashim Mandal*

SR Department of Anesthesiology, Bankura Sammilani Medical college and Hospital, West Bengal. *Corresponding Author

Dr. Partha Sarathi Mondal

Senior Resident, Department of Neurosurgery, PGIMER, CHANDIGARH.

Dr. Debarshi Jana

Institute of Post-Graduate Medical Education and Research, A.J.C. Bose Road, Kolkata, West Bengal, India-700020.

ABSTRACT

Brain tumours may cause disturbances of cerebral auto-regulation & the blood brain barrier (BBB). These effects could possibly have an unfavourable influence on brain condition.

To compare the effects of the application of a bolus hypertonic saline with those of mannitol on intraoperative brain relaxation.

Ninety patients of ASA grade II and III in the age group >18 years with supratentorial brain tumours posted for elective brain tumour surgery were studied in the current study. They were randomly allocated into two groups.

Each group enrolled with 45 patients-

Group HTS: receiving 160 ml of 3% hypertonic saline.

Group M: receiving 150 ml of 20% mannitol.

Patients from both groups were induced with injection fentanyl, propofol & rocuronium. Maintained with N₂O: O₂ in a ratio of 2:1 combined with isoflurane, fentanyl and vecuronium. End tidal CO₂ pressure were maintained between 35-40 mm Hg. Arterial blood pressure were kept within baseline value $\pm$ 20.

Hence application of hypertonic saline is a more effective method for brain relaxation in patients posted for elective supratentorial brain tumours surgery and can be a great value in routine practice.

KEYWORDS

Hypertonic Saline, Mannitol, Brain Relaxation, Elective Supratentorial

INTRODUCTION

Brain tumours may cause disturbances of cerebral auto-regulation & the blood brain barrier (BBB). These effects could possibly have an unfavourable influence on brain condition.

Medical management of brain relaxation is a critical component of anesthesia during the neurosurgical procedures. Cerebral swelling (or unsatisfactory brain relaxation) is the common clinical situations in patients undergoing craniotomy, which may make the surgical exposure and operative procedure more difficult, and greatly increase the risk of poor outcome if associated with localized cerebral ischemia. Thus, there is increasing investigation worldwide exploring the ideal therapy to get satisfactory brain relaxation during the neurosurgical procedures.

It is well-known that various methods including hyperventilation, drainage of cerebrospinal fluid (CSF), and usage of hyperosmotic agents have been used during neurosurgery to control brain relaxation. Mannitol is considered as the standard and a first choice hyperosmotic agent for the treatment of brain relaxation in a variety of intracranial diseases.

However, a wealth of clinical studies have reported that many patients with tight brain are refractory to the mannitol. Vigorous and repeated administration of mannitol may lead to obvious side effects involving excessive diuresis, electrolyte abnormalities and secondary hypovolemia, while the latter is undesirable in patients undergoing neurosurgical procedures because it may result in intraoperative hypovolemic. These issues have lead to increasing enthusiasm about the development of alternative approaches in hyperosmotic therapy during neurosurgical procedures.

The first idea of osmotherapy for central nervous system (CNS) diseases came about in 1919 when two research fellows from Reed Army Medical Centre working at Johns Hopkins medical school observed that the intravenous injection of 30% saline solution in anaesthetized cats lead to a 3-4mm reduction in brain size, lasting 15-30 min after each injection.

In recent years, hypertonic saline (HS) has emerged as an attractive

alternative in hyperosmotic management to get satisfactory brain relaxation in a variety of neurosurgical practices. A number of prospective clinical trials comparing the effects of hypertonic saline with mannitol on the intracranial pressure have suggested that hypertonic saline is at least as effective as, if not better than, mannitol in the treatment of intracranial hypertension. Moreover, a recent systematic review of hypertonic saline compared to isotonic solution for peri-operative fluid management indicates hypertonic saline can reduce the volume of intravenous fluid required to maintain patients undergoing surgery. The intravascular support mechanism of hypertonic saline may mainly involve its ability to shift fluid from interstitium to intravascular space to counteract perioperative hypotensive effects.

Thus, in situations such as during neurosurgical procedures where large volume of fluid administration may be accompanied by increased risk of cerebral swelling and intracranial hypertension, a role for hypertonic saline is emerging. With the publication of recent literatures involving hypertonic saline and mannitol, it is possible for us to further compare the effects of hypertonic saline with mannitol during the neurosurgical procedures. The present meta-analysis is performed to determine the benefits and harms of hypertonic saline versus mannitol administered to the patients undergoing craniotomy during elective neurosurgical procedures for supratentorial brain tumour.

1. Primary Aim:- to compare the effects of the application of a bolus hypertonic saline with those of mannitol on intraoperative brain relaxation.

2. Secdonary Aim:- intensive care unit(ICU) stays and hospital days.

MATERIALS AND METHODS

After obtaining the approval from ethical committee of S.C.B. Medical College & Hospital and written informed consent from patients, we performed a power calculation to determine the ideal sample size before initiation of the study. We enrolled a minimum of 45 patients in each group.

Ninety patients who were scheduled to undergo elective craniotomy for supratentorial brain tumors were enrolled in this prospective,

randomized, and double-blind study. The data were collected between August 2013 and August 2015 at neurosurgery department of S.C.B. medical college & hospital.

Ninety patients were randomly allocated into two group:-

Group HTS (n 45) : receiving 160 ml of 3% hypertonic saline.

Group M (n 45) : receiving 150 ml of 20% mannitol.

Exclusion Criteria

1. Age <18 years,
2. ASA physical status IV–V,
3. Signs of increased intracranial pressure, peri-operative hypo or hyper-natremia (serum sodium <135 or >150mEq/L, respectively),
4. History of treatment with any hyperosmotic fluids (HTS or mannitol) within the 24 hours preceding the surgery,
5. History of congestive heart failure or severe renal function impairment.

Thorough pre anesthetic evaluation including case history, physical examination, airway examination were done before surgery. All routine investigation including hemoglobin (Hb), packed cell volume (pcv), total leucocyte count (TLC), differential count (DC), clotting time (CT), bleeding time (BT), fasting blood sugar (FBS), serum sodium, potassium, urea, creatinine, and liver function test (LFT) were done and written informed consent was taken from all patients. All the patients were kept nil per oral for 8 hrs before surgery. All patients received 10 mg dexamethasone intra-venous every 6 hours for 48 hours before brain tumor resection.

On the day of surgery, after arrival of patient to the operation theatre, pulse-oxygenator, electro-cardiogram (ECG), and non-invasive blood pressure monitors were connected. After randomization using sealed envelopes, patients were assigned to receive intravenous administration of equiosmolar hyperosmotic fluids, either 160 mL of 3% HTS (group HTS) or 150 ml of 20% mannitol (group M) for 5 minutes using an infusion pump at the time of scalp incision via central line. The surgeons and anesthesiologists were blinded to the identity of the agents under study.

General anesthesia was induced with injection fentanyl (2 microgm/kg), propofol (2 mg/kg), and rocuronium (1 mg/kg) using a peripheral intravenous line. In addition to standard monitoring, we placed a central venous catheter. Anesthesia was maintained with nitrous oxide (N₂O): oxygen (O₂) in a ratio of 2:1 combined with inhalation of isoflurane and intra-venous infusion of fentanyl (1 micro gm /kg/hr) and vecuronium (1 micro gm/kg/min), which were administered at the attending anesthesiologist's discretion.

Statistical Analyses

Data are presented as the mean±sd (standard deviation) or as the median with ranges. One-way analysis of variance with repeated measures and paired Student "t" test were used for the analysis of data within each group (fluid input, urine output, and hospital days). Differences between the HTS and M groups were analyzed using a X² test (demographic variables), a Mann-Whitney U test (brain relaxation scores), and an unpaired Student t test with Bonferroni correction for multiple measurements (fluid input, urine output, blood loss, and hospital days). A multivariate analysis of variance was used for the comparison of changes in serum sodium over time between the groups. P value <0.05 was considered significant. All statistical tests were performed on a windows based computer using the program SPSS 22.0.

OBSERVATION

Our study showed that there were no significant differences between the 2 groups regarding age, sex, severity of illness. Differences between the HTS and M groups were analyzed using a X² test (demographic variables).

We found that there were no significant differences between the 2 groups regarding height and weight. Differences between the HTS and M groups were analyzed using a X² test (demographic variables).

It was found that the number of brain conditions classified as soft, adequate, and tight in the HTS group was 28, 13, and 4, respectively, whereas it was 15, 20, and 10, respectively, in the M group. Brain relaxation was significantly better in the HTS group compared with the M group. Differences between the HTS & M groups were analyzed using a Mann-Whitney U test.

We also found that there was no significant difference regarding fluid input before opening the dura between the two groups. Difference between the HTS and M group was analysed using an unpaired student t-test with Bonferroni correction for fluid input.

It was found that there were no significant differences regarding total fluid input between 2 groups. Differences between the HTS and M groups were analyzed using an unpaired Student t test with Bonferroni correction for fluid input. There were no significant differences between the 2 groups regarding anaesthetic time and operation time. Paired student t test were used for the analysis of data within each group.

Our study showed that urine output was higher in the M group compared with the HTS group. Paired student t test was used for the analysis of data within each group regarding urine output. Compared with mannitol, hypertonic saline caused an increase in serum sodium concentration over time. Difference between 2 groups were analysed by using student t-test.

DISCUSSION

As brain relaxation is a critical component of anesthesia during the neurosurgical procedures, good management of brain relaxation and intracranial pressure is very important for the neurosurgeons. Satisfactory brain relaxation can facilitate the surgical access and lesion removal during neurosurgery while cerebral swelling and increased intracranial pressure can seriously jeopardize surgical access and increase the risk of poor outcome and neurological deficits.

Both mannitol and hypertonic saline have proven to be effective at controlling brain relaxation, through osmotic dehydration of cerebral interstitium, reduction of blood viscosity, increased red blood cell deformation, and improved microcirculation.

In our randomized study, we demonstrated that-

1. 3% hypertonic saline provided a more satisfactory brain relaxation than did mannitol.

In 2011, **Wu** published a prospective randomized double blind study and they concluded that brain relaxation with use of 3% hypertonic saline was more satisfactory than with 20% mannitol, which was similar with our study.

In 2007, **Rozet et al.** published a prospective double-blind randomized study on the effect of equiosmolar solutions of mannitol versus hypertonic saline on intraoperative brain relaxation and electrolyte balance. They recommend that hypertonic saline is a safe alternative to mannitol in brain size reduction.¹

Gemma et al.² reported that hypertonic saline and mannitol provide satisfactory cerebral relaxation in patients taken to elective craniotomy. This study was conducted with different neurosurgical procedures and non-equiosmolar doses of hypertonic saline and mannitol.

De Vivo et al.³ conducted a prospective randomized comparative study in supratentorial tumours. They concluded that hypertonic saline is an effective alternative for lowering intracranial pressure in humans without reducing central venous pressure or serum osmolality.

In 2003, **Vialet et al.**⁴ conducted a randomized prospective study to evaluate the clinical benefit of using hypertonic saline in refractory intracranial hypertension episodes. They compared 20% mannitol and 7.5% hypertonic saline in patients with traumatic brain injury and refractory intracranial hypertension (ICP = 25 mmHg). Although they found no difference in clinical outcomes.

Kamel,⁵ carried out a meta-analysis of all randomized trials comparing mannitol and hypertonic saline for the treatment of intracranial hypertension. The conclusion was that hypertonic saline may be more effective than mannitol for the treatment of intracranial pressure elevation.

The physical effects of hypertonic saline and mannitol on the brain of patients with normal intracranial pressure have been investigated.^{3,6} The effectiveness of the hyperosmolar solute depends on its "reflection coefficient" (RC), which determines the relative impermeability of an intact blood brain barrier to the solute. An RC of 1 means an absolutely

impermeable solute and an RC of 0 means an ideally permeable solute. Hypertonic saline may present a theoretical advantage over mannitol because sodium has a higher osmotic RC than does mannitol (1.0 vs 0.9). A lower solute leakage may evoke a greater increase in serum osmolality, and a higher trans-endothelial osmotic gradient in the vascular compartment may lead to increased brain water extraction into the intravascular space. In addition, a lower RC contributes to lower incidence of rebound cerebral edema. In this regard, our data revealed a more effective brain-bulk reduction associated with hypertonic saline versus mannitol, which is consistent with the classic theory of hyperosmotic therapy.

Administration of hypertonic saline or mannitol increases serum sodium concentration or osmolality and decreases intracranial pressure and brain water content in non-injured brain areas, as shown in human and animal studies.⁷⁻¹⁰ The principal mechanism underlying these effects is the induction of a water shift from brain tissues to the intravascular space by the hyper-osmolality of hypertonic saline and mannitol because the blood brain barrier (BBB) is impermeable to sodium and mannitol.

2. 3% HTS was associated with a significantly higher level of serum sodium compared with mannitol.

3. Compared with 3% hypertonic saline, mannitol had a more prominent diuretic effect.

Our study showed that 3% hypertonic saline was associated with significantly higher levels of serum sodium and a decreased diuretic effect compared with mannitol, which is compatible with the results of **Rozet et al.**¹¹ The increase in serum sodium stimulates the release of antidiuretic hormones, leading to the absorption of free water from the kidney, which may explain the lower diuretic effect of hypertonic saline compared with mannitol. In addition, **Rozet et al.**¹¹ reported that mannitol had a more prominent diuretic effect and a less positive or even negative fluid balance, which was associated with an increase in blood lactate overtime, whereas no changes in blood lactate were observed after hypertonic saline administration. The negative fluid balance induced by mannitol suggests that the increase in lactate concentration may be secondary to effective hypovolemia and hypovolemia is considered detrimental after brain injury. So hypertonic saline have gained renewed interest and, recently, are administered more frequently in neurocritically ill patients.

Together with the hyperosmotic mechanism, the improved blood rheology with shrinkage of erythrocytes, the decreased cerebrospinal fluid production, and the anti-inflammatory and other lesser properties associated with both hypertonic saline and mannitol are believed to play a role in their therapeutic action on healthy and injured brains. However, it has become popular to view hypertonic saline as having some advantages over mannitol. **Oddo et al.**¹² examined the effects of mannitol (25%, 0.75 g/kg) and hypertonic saline (7.5%, 250mL) on brain tissue oxygen tension in 12 patients with refractory intracranial hypertension. They showed that if these patients exhibited a poor response to previous mannitol treatment, the administration of 7.5% hypertonic saline as the second-tier therapy was associated with a significant increase in brain oxygenation and improved cerebral and systemic hemodynamics.

Heimann et al.¹³ showed hypertonic saline improved cerebral blood flow and reduced the area of infarction by using a laser Doppler approach in a rat cerebral ischemia model.

Moreover, **Taylor et al.**¹⁴ used a near-infrared spectrophotometer to show that cerebral oxygenation was restored more rapidly in the hypertonic saline-treated group in a pediatric animal model of head injury and hemorrhagic shock. The comparison of hypertonic saline and mannitol revealed that the former seems to favor intracranial pressure reduction, brain circulation, cerebral oxygenation, and hemodynamic stability. In addition, hypertonic saline was associated with more pronounced increase in osmolality, and decrease in intracranial pressure (ICP), which improve brain swelling and cerebral perfusion and attenuate the progression of secondary brain injury. Therefore, it was reasonable to presume that the hypertonic saline group would exhibit improved outcomes.

4. Intensive care unit (ICU) stays and hospital days were similar between the 2 groups after elective supratentorial brain tumor surgery. The results of ICU stays and hospital days in the two groups were

similar, perhaps because

a. These study outcomes were affected mainly by the factors described above, rather than by the different effects of hypertonic saline and mannitol on brain relaxation.

b. Significant differences may have been present mainly at the cellular level or at the cognitive function level, which was beyond the scope of our study.

c. Even though hypertonic saline yielded a greater effect on brain relaxation, it is very important to note that a reduction in brain volume does not necessarily translate into a better cerebral outcome; and the median intensive care unit (ICU) stays and hospital days was just 2 and 8 days, respectively.

Violet et al.⁴ did not find differences, in term of mortality rate or neurological outcomes at 90 days.

Although serious complications were not observed, the prognosis of brain tumor surgery was influenced by many factors, including the size and the location of the tumor, the severity of the adjacent tissue damage, the residual function after tumor excision, and the immune or inflammatory responses to the procedure.

Throughout the procedure, we maintained end tidal carbon-di-oxide between 35 and 40 mm Hg and arterial blood pressure (ABP) within baseline values $\pm 20\%$ to avoid the effect of carbon-di-oxide and arterial blood pressure on brain bulk until assessment by the surgeon. It is possible that arterial blood pressure (ABP) fluctuations were manipulated by the blinded anesthesiologist; however, this is unlikely because no specific hemodynamic pattern emerged before the surgical appraisal. We did not measure intracranial pressure routinely during elective supratentorial brain tumor surgery in clinical practice. Although brain relaxation can be influenced by intracranial pressure, hence patients with signs of increased intracranial pressure were excluded from the study. Hypertonic saline have evolved as an alternative to mannitol or may be used to manage otherwise refractory intracranial hypertension. Caution is advised for high osmolar fluid loads because they are associated with an increased risk of the potentially deleterious consequences of hypernatremia or may induce osmotic blood brain barrier (BBB) opening, with possible harmful extravasation of the hypertonic solution into the brain tissue. However, if administered via an appropriate route and at an appropriate dose, it is no more dangerous than other similar drugs, including mannitol.

Therefore, randomized outcome trials comparing mannitol with hypertonic solution in various subpopulations of patients with neurologic injury would provide valuable information and a basis for the establishment of the most adequate clinical applications.

This prospective, double-blind, randomized human study demonstrates the differential effects of hypertonic saline and mannitol on intraoperative brain relaxation. This study is also unique for using a design that correlates drug administration with intensive care unit stays and hospital days. We think that this study design provides an opportunity to test the effect of equiosmolar 3% hypertonic saline and 20% mannitol on brain relaxation under a uniform type of intracranial surgery.

Within the limitations of this study, these data allowed us to conclude that equiosmolar 3% hypertonic saline provided more satisfactory brain relaxation (compared with 20% mannitol) during elective supratentorial brain tumor surgery.

CONCLUSION

It was found that brain relaxation was significantly better in group HTS compared with group M. Increase in serum sodium concentration is more in group HTS and urine output is higher in group M. Regarding intensive care unit (ICU) stays and hospital days there were no significant difference between two groups.

We did not come across any marked complication.

From the current study it can be concluded that (1) 3% hypertonic saline provided a more satisfactory brain relaxation than did mannitol; (2) 3% hypertonic saline was associated with a significantly higher level of serum sodium compared with mannitol; (3) compared with 3% hypertonic saline, mannitol had a more prominent diuretic effect; and (4) ICU stays and hospital days were similar between the 2 groups after elective supratentorial brain tumor surgery.

Hence application of hypertonic saline is a more effective method for

brain relaxation in patients posted for elective supratentorial brain tumours surgery and can be a great value in routine practice.

Distribution of mean Age(yrs), Height (cm), Weight(kg), Duration of surgery, Urine Output and Na⁺ conc.

	Variables	Group HTS	Group M	P value
Patients characteristics	Age(yrs)	45.02±11.6	45±9.6	0.98
	Height (cm)	164.16 ± 13.32	159 ± 11.4	0.12
	Weight(kg)	55.04 ± 3.91	54.38 ± 3.84	0.42
Duration of surgery	Anaesthesia time(min)	254.18 ± 26.62	264.67 ± 23.21	0.19
	Operation time(min)	239.53 ± 14.12	239.67 ± 14.75	0.96
	Total urine output(ml)	593.78 ± 45.52	713.56 ± 34.46	0.02
Na ⁺ conc.	Baseline	138.04±0.67	138.06±0.85	0.89
	At dura opening	144.73 ±0.8	131.91±0.89	<0.001
	1 hr	143.02±0.58	134.51±0.54	<0.001
	2 hr	141.29±0.65	136.24±0.74	<0.001
	3 hr	140.84±0.71	137.58±0.68	0.04
	4 hr	140.78±0.69	138.47±0.62	0.04
	5 hr	139.11±0.87	137.16±0.58	0.03

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