A COMPARISON OF THREE DIFFERENT DOSES OF MANNITOL ON BRAIN RELAXATION DURING SUPRATENTORIAL BRAIN TUMOUR CRANIOTOMY

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ABSTRACT

BACKGROUND

A comparison of three different doses of mannitol on brain relaxation during supratentorial brain tumour craniotomy. Supratentorial tumours produce significant mass effects in the brain and certain types are accompanied by significant peritumoral oedema that leads to increased intracranial pressure. Higher osmotic pressure in the blood vessels after the infusion of mannitol drives water molecules from the brain tissue to blood vessels and results in brain tissue dehydration. The point of my study is to determine a dose that leads to a beneficial effect without triggering negative effects.

MATERIALS AND METHODS

This is a prospective, randomised single-blinded study conducted in Konaseema Institute of Medical Sciences, Amalapuram, from March 2015 to March 2017. After getting ethical committee approval and informed consent, 48 patients of both sexes (male and female) who underwent elective craniotomy for supratentorial tumour surgeries under general anaesthesia at were taken up for study. 48 patients were divided into three groups as group-A, group-B and group-C with 16 in each group.

RESULTS

There is significant change in brain relaxation score with increasing dose of mannitol. MAP and pH are significant with increasing dose of mannitol, serum sodium and potassium levels are also significant. Anion gap and urine output also showed significant change. Age, sex and BMI are not statistically significant.

CONCLUSION

From this study, it is concluded that 1.5 mg/kg of 20% mannitol gives better brain relaxation scores than 0.5 mg/kg of 20% mannitol and 1.0 mg/kg of 20% mannitol.

KEYWORDS

Mannitol, Brain Relaxation, Supratentorial Tumours.

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BACKGROUND

Most of the brain tumours are supratentorial tumours accounting for 79% of all tumours.The most common of which gliomas, meningiomas and pituitary tumours produce significant mass effects in the brain and certain types are accompanied by significant peritumoral oedema that leads to increased intracranial pressure. Bedford et al[1] showed that the preoperative degree of peritumoural oedema was closely related to the postoperative increase in intracranial pressure. Rasmussen et al[2] revealed that the risk of brain dura opening was very high in 692 cases of patients with glioma with midline shift undergoing craniotomy, this result indicated that in cases with preoperative increased intracranial pressure. Dehydration aids in ensuring proper brain relaxation and facilitates tumour exposure. Higher osmotic pressure in the blood vessels after the infusion of mannitol drives water molecules from the brain tissue to blood vessels and results in brain tissue dehydration.[3] If the BBB is damaged, mannitol will extravasate outside the blood vessels and will transfer water molecule into brain tissue, which will aggravate cerebral oedema and increased intracranial pressure. There may be some degree of BBB disruption in certain patients, which would prevent the desirable effects of mannitol; however, the extent of this disruption is unclear and often affected by multiple-dose mannitol. The use of mannitol for the type of surgery that patients in our study will undergo has been found overall to be beneficial; however, the appropriate dose of mannitol is controversial, particularly since large multiple dose can have

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negative effects.[4] Some clinicians advocate high dose (>1.0 gm/kg) of mannitol to effectively reduce intracranial pressure, while other recommend lower dose (<1.0 gm/kg). But, recently clinicians advocate still high dose of mannitol up to 1.5 gm/kg to effectively reduce intracranial pressure. Treatment guidelines for using mannitol in patients undergoing supratentorial brain tumour craniotomy have been published and provide recommendations regarding the dose and timing of mannitol. However, there is still controversy concerning dehydration treatment with mannitol in patients with preoperatively increased intracranial pressure during brain tumour surgery. More recently, a prospective randomised controlled study demonstrated that a single dose of 0.5 gm/kg or 1.4 gm/kg mannitol achieved similar brain relaxation in patients undergoing supratentorial brain tumour craniotomy and tumour resection. However, further statistical analysis that took into account the preoperative midline shift indicated that the high dose yielded better outcome.

The study indicated that the effect of mannitol on brain relaxation maybe dose-dependent if the preoperative increase in intracranial pressure is taken into consideration; however, further study is required to verify this suggestion. The point of my study is to determine a dose that leads to a beneficial effect without triggering negative effects.

Primary Aim of the Study

To compare three different doses of 20% mannitol (0.5 gm/kg, 1.0 gm/kg and 1.5 gm/kg) on brain relaxation during supratentorial brain tumour craniotomy.

Secondary Aim of the study

1. To evaluate changing haemodynamic stability following different doses of mannitol administration.
2. To evaluate changing PH following different doses of mannitol administration.
3. To evaluate changing electrolytes following different doses of mannitol administration.

MATERIALS AND METHODS

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Groups	Assigned Interventions
Group A	
20% mannitol 0.5 gm/kg	Drug- Mannitol
Study subjects will be randomised to receive an infusion of 20% mannitol 0.5 gm/kg over 30 minutes after induction	Variation of mannitol dose
Group B	
20% mannitol 1.0 gm/kg	Drug- Mannitol
Study subjects will be randomised to receive an infusion of 20% mannitol 1.0 gm/kg over 30 minutes after induction	Variation of mannitol dose
Group C	
20% mannitol 1.5 gm/kg	Drug- Mannitol
Study subjects will be randomised to receive an infusion of 20% mannitol 1.5 gm/kg over 30 minutes after induction	Variation of mannitol dose

Inclusion Criteria

1. Patients who are undergoing an elective craniotomy for supratentorial tumours under GA.
2. 18-60 yrs.
3. Male/Female.
4. ASA 1-3.

Exclusion Criteria

1. Pregnancy.
2. Congestive heart failure.
3. Chronic renal failure.
4. Recent use (<24 hrs. before surgery) of mannitol or other hypertonic solution.

In the preoperative waiting room, detailed history and physical examination was done. Basic investigations were collected. Baseline data like pulse rate, blood pressure, SpO2, temperature, serum electrolytes and preoperative arterial blood gases were recorded. Group A, Group B and Group C were explained about the procedures and follow up pattern. A standardised anaesthetic technique was used.

All patients were premedicated with inj. glycopyrrolate 0.2 mg intramuscularly 45 minutes before surgery. Monitors were connected. Intravenous cannula secured and connected to IV fluids. Another intravenous cannula secured for infusion of 20% mannitol. Patients were preoxygenated with 100% O2 for 3 minutes. Patients were induced with injection fentanyl 2 micrograms per kilogram of body weight, thiopentone 5 milligrams per kilogram of body weight, injection succinylcholine was avoided in my study, because to avoid rise in intracranial pressure. For that injection, vecuronium of 0.08 milligrams per kilogram for body weight was used. To blunt the intubation response injection, 2% lignocaine of 1.5 mg/kilogram was given intravenously. Patient were intubated with 7 size/7.5 size endotracheal tube for female and 8 size/8.5 size endotracheal tube for male was used.

Bilateral air entry checked and connected to closed circuit. Patients is maintained with N_2O:O_2 with injection fentanyl 1 microgram per kilogram of body weight every 45 minutes and injection vecuronium in titrated doses. Haemodynamic variables like blood pressure, mean arterial pressure, pulse rate and SpO2 were measured immediately prior to the infusion of mannitol at 30 and 60 minutes after the administration of mannitol. Similarly, urine output, perioperative fluid balance, blood loss and laboratory datas like blood gases were measured immediately prior to the infusion of mannitol at 30 and 60 minutes after the administration of mannitol. Data were recorded according to the time frame. At the time opening dura mater, brain relaxation was assessed by a senior neurosurgeon on scale from 1 to 4, which was given as follows.

At the end of surgery, after adequate attempts of respiration patients were reversed with injection glycopyrrolate of 10 micrograms per kilogram of body weight and injection neostigmine of 40 micrograms per kilogram body weight. Adequate suctioning done. To blunt the extubation response injection 2% lignocaine of 1.5 gm/kilograms was given. Patients were then extubated after gaining adequate muscle power.

Parameters Monitored Intraoperatively
Primary Outcome Measures

- Brain relaxation at the opening of the dura mater assessed by a senior surgeon on scale (Rozet Quentin scale) from 1 to 4.
- Scale 1- Perfectly relaxed (shrunken dura with prominent veins).
- Scale 2- Satisfactorily relaxed (only prominent veins).
- Scale3- Firm brain.
- Scale 4- Bulging brain.
- Time frame- At the opening of the dura mater.

Secondary Outcome Measures
Haemodynamic Variables
MAP, heart rate, BP, SpO2.
Time frame- Immediately prior to the infusion of the mannitol at 30 and 60 minutes after the administration of mannitol.

Urine Output
Time frame immediately prior to the infusion of the mannitol at 30 and 60 minutes after the administration of mannitol.

Perioperative Fluid Balance and Blood Loss
Time frame- Immediately prior to the infusion of the mannitol at 30 and 60 minutes after the administration of mannitol.

Laboratory
Blood gases, electrolytes, time frame- Immediately prior to the infusion of the mannitol at 30 and 60 minutes after the administration of mannitol.

OBSERVATION AND RESULTS

20% Mannitol	Before	30 Mins.	1 Hr.
0.5 gm	4	3.46	3.4
1.0 gm	4	3	2.8
1.5 gm	4	1.11	1.03
P-value	1.00 NS	<0.001 sig.	<0.001 sig.
Table 1. Brain Relaxation Score			

a. In this brain relaxation score, p value is less than 0.005.
b. There is significant change in brain relaxation score with increasing dose of mannitol.

20% Mannitol	Before	30 Mins.	1 Hr.
0.5 gm	110	105	100
1.0 gm	110	90	85
1.5 gm	110	80	70
P-value	1.00 NS	<0.001 sig.	<0.001 sig.
Table 2. Mean Arterial Blood Pressure			

a. In this mean arterial blood pressure, p value is less than 0.005.
b. There is significant change in mean arterial blood pressure with increasing dose of mannitol.

20% Mannitol	Before	30 Mins.	1 Hr.
0.5 gm	7.44	7.4	7.38
1.0 gm	7.44	7.38	7.36
1.5 gm	7.44	7.34	7.32
P-value	1.00 NS	<0.001 sig.	<0.001 sig.
Table 3. Arterial Blood Gas Analysis-PH			

a. In this arterial blood gas analysis-PH, P value is less than 0.005.
b. There is significant change in arterial blood gas analysis-PH value with increasing done of mannitol.

20% Mannitol	Before	30 Mins.	1 Hr.
0.5 gm	144	139	139
1.0 gm	144	138	137
1.5 gm	144	134	132
P-value	1.00 NS	<0.001 sig.	<0.001 sig.
Table 4. Arterial Blood Gas Analysis-Sodium			

a. In this arterial blood gas analysis - sodium, p value is less than 0.005.
b. There is a significant change in arterial blood gas analysis-sodium value with increasing dose of mannitol.

20% Mannitol	Before	30 Mins.	1 Hr.
0.5 gm	4.5	4.3	4.1
1.0 gm	4.5	4	3.8
1.5 gm	4.5	3.8	3.3
P-value	1.00 NS	<0.001 sig.	<0.001 sig.
Table 5. Arterial Blood Gas Analysis- Potassium			

a. In this arterial blood gas analysis- potassium, p value is less than 0.005.
b. There is significant change in arterial blood gas analysis-potassium value with increasing dose of mannitol is maintained within the acceptable range of arterial blood gas analysis- potassium value.

20% Mannitol	Before	30 Mins.	1 Hr.
0.5 gm	13	12	11
1.0 gm	13	11	10
1.5 gm	13	9	10
P-value	1.00 NS	<0.001 sig.	<0.001 sig.
Table 6. Arterial Blood Gas Analysis- Anion Gap			

a. In the arterial blood gas analysis- Anion gap, P value is less than 0.005.
b. There is a significant change in arterial blood gas analysis- Anion gap value with increasing dose of mannitol.

20% Mannitol	Before	30 Mins.	1 Hr.	P-value
0.5 gm	72.71	390.29	547.57	<0.001
1.0 gm	72.28	745.86	983.43	<0.001
1.5 gm	71.14	1294.57	1646.71	<0.001
Table 7. **Urine** ***Output***				

a. In this urine output - P value is less than 0.005.
b. There is a significant change in urine output value with increasing dose of mannitol.

20% Mannitol	Before	30 Mins.	1 Hr.
0.5 gm	38.5	38.3	37.8
1.0 gm	38.5	38.2	37.7
1.5 gm	38.5	38.3	37.8
P-Value	**1.00 NS**	**0.80 NS**	**0.90 NS**
Table 8. **Temperature**			

a. In this temperature measurement, P value is more than 0.005.
b. There is no significant change in temperature.

20% Mannitol	Before	30 Mins.	1 Hr.	P-value
0.5 gm	40.2	40.2	40.2	1
1.0 gm	40.5	40.5	40.5	1
1.5 gm	44	44	44	1
Table 9. Age				

a. In this age distribution, p value is 0.344, which is more than 0.005.
b. Age distribution shows statistically not significant difference.

20% Mannitol	Before	30 Mins.	1 HR	P-value
0.5 gm	24.14	24.14	24.14	1
1.0 gm	31.03	31.03	31.03	1
1.5 gm	25.6	25.6	25.6	1
Table 10. Body Mass Index Measurement				

a. In this body mass index measurement, P value is 0.403, which is more than 0.005.
b. Body mass index measurement shows statistically not significant difference.

20% Mannitol	Before		30 Mins.		1 Hr.	
Sex	Male	Female	Male	Female	Female	Female
0.5 gm	23	12	23	12	23	12
1.0 gm	16	19	16	19	16	19
1.5 gm	21	14	21	14	21	14
Table 11. Sex						

a. In this sex distribution, P value is 0.653, which is more than 0.005.
b. Sex distribution show statistically not significant difference.

DISCUSSION

Mannitol is often recommended as the first choice hyperosmotic drug to treat increased Intracranial Pressor (ICP) and alleviate brain bulk during intracranial surgery. However, the optimal administration and dosage of mannitol for brain relaxation remain controversial, especially in patients with preoperative increased ICP. Previous prospective randomised trials have focus on the relationship between mannitol and intraoperative brain relaxation; however, none of these trials examined how different doses of mannitol influenced brain relaxation in patients with a preoperative brain midline shift.

The main side effect of mannitol include electrolyte abnormalities (for example hypokalaemia) and renal cardiac dysfunction. Patients with heart failure, pulmonary oedema, electrolyte imbalance, chronic hypertension, coronary heart disease and diabetes often have renal dysfunction without clinical manifestations.

During the operation, the neurosurgeon will decide whether to initiate treatment for brain bulk via the assessment of intraoperative brain relaxation, which is not an objective sign, such as ICP. Treatments for improving brain relaxation include adjusting the ventilator to induce hyperventilator expanding the surgical incision site and infusing mannitol. These procedures contribute to tumour exposure and excision. Thus, these subjective assessment of degree of brain relaxation can be used as a diagnostic criteria prior to treatment Sorani et al[6] performed a retrospective study to characterise the dose-response relation between mannitol and ICP in intensive care unit patients with traumatic brain injuring and found that the degree and incidence of peritumoral oedema greatly varied. Therefore, it is not appropriate to measure the effect of mannitol in patients which can exacerbate this dysfunction and lead to kidney injury. Cardiac preload and central venous pressure increase 5 to 15 mins. after mannitol is administered.[7] The diuretic effects of mannitol may cause water and electrolyte imbalance, hypotension and decreased

plasma concentration of sodium, potassium and chlorine. As shown in other studies, increased doses of mannitol resulted in an increase in osmolarity, a decrease in serum sodium concentration and an increase in urine output.

The development of hyponatraemia can be explained by the changes in osmolarity and the initial volume shift toward the intravascular compartment along the osmolar gradient and the resulting hemodilution. Higher doses of mannitol result in a dose-related increase in osmolarity as well as a similar dose-related decrease in brain water content. This result in better relaxation score in patients with traumatic brain injury.[8]

Mannian et al[9] described a significant increase in the serum potassium level, which reached a maximum mean increase of 1.5 mmol/L, after high-dose mannitol (1.5 g/kg) administration in seven patients undergoing cerebral aneurysm clipping.[10] Therefore, patient's supratentorial tumours including gliomas and meningiomas using brain water content.

In this prospective randomised trial, we will observe the effects of different doses of mannitol on patient outcomes three months postoperatively. Patients undergoing craniotomy commonly have complications that include postoperative cerebral oedema, cerebral haemorrhage, recurrence and even death, which are closely related to intraoperative tumour exposure, resection and sufficient coagulation. The incidence of postoperative complications determines the length of intensive care unit and hospital stay as well as patient outcome. Mannitol may help improve tumour exposure and resection. However, if the BBB is damaged, mannitol will be transferred from the ruptured or highly permeable blood vessels into brain tissue, which reverses the osmotic pressure difference and results in brain oedema. Animal studies demonstrated that five repeated doses of mannitol lowered ICP and reduced cerebral oedema; however, oedema increased following greater exposure to mannitol.

Based on the current literature, we propose that different doses of mannitol will improve brain relaxation as well as ease surgical exposure in a dose-dependent manner for patients with preoperative midline shift undergoing elective supratentorial brain tumour surgery. The risk of brain swelling after dural opening is high in patients with midline shift undergoing supratentorial tumour surgery. Brain swelling may result in increased intracranial pressure, impeded tumour exposure and adverse outcome.

Mannitol is recommended as a first line dehydration treatment to reduce brain oedema and enable brain relaxation during neurosurgery. Research has indicated that mannitol enhanced brain relaxation in patients undergoing supratentorial tumour surgery; however, these results need further confirmation and the optimal mannitol dose has not yet been established. Purpose to examine whether different doses of 20% mannitol improve brain relaxation in a dose-dependent manner when administrated at the time of incision.

Quentin et al[11] examined the effects of two doses (0.5 and 1.5 g/kg) of mannitol on brain relaxation in tumour patients, neither of which was the routine clinical dose (1 g/kg). Additionally, they did not consider the effect of the preoperative intracranial mass. However, these studies indicated that the effect of mannitol on brain relaxation was dose-dependent and higher doses 1.5 gm/kg of body weight gives better brain relaxation than lower dose of 0.5 gm/kg of body weight of 20% mannitol. The current proposal is a prospective randomised controlled study that aims to examine the effect of three doses of mannitol on brain relaxation in patients with preoperative midline shift.

CONCLUSION

a. In this study, from the data and statistical analysis, it is concluded that 1.5 mg/kg of 20% mannitol gives better brain relaxation scores than 0.5 mg/kg of 20% mannitol and 1.0 mg/kg of 20% mannitol.
b. Serum electrolytes, blood gases, urine output and haemodynamic stability are better maintained without gross impairment in 1.5 mg/kg of 20% mannitol.
c. Age, sex and BMI did not influence the study results.

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