Study Protocol

Comparative Evaluation of efficacy of Mannitol and Hypertonic Saline (3%) for treatment of moderate to severe Traumatic Brain Injury (TBI)

Abstract:

Background: Intracranial Pressure of higher than 20 mm of Hg is considered Intracranial Hypertension. For years, Mannitol has been the go-to drug for its cure. However, it has many adverse effects. Therefore, other drugs are being considered for reducing Intracranial Pressure (ICP), and hypertonic saline (HTS) appears to be a good alternative.

Objectives: The reason for this study is to report any differences in results after using of mannitol or hypertonic saline for treating Intracranial Hypertension (IH) in patients who were in the tertiary care hospital to be treated of moderate or severe Traumatic Brain Injury (TBI).
Methodology: All patients who had moderate or severe Traumatic Brain Injury (TBI) i.e, were reported at the hospital and had Glasgow Coma Score lesser than 13, were admitted in the hospital over the course of 2 months of the study will be included. Patients will be randomized into 2 statistically comparable groups. Group A and Group B will be given the standard amount of mannitol and hypertonic saline (3%) and clinical result will be noted for both cases.

Results: The results will be calculated by rate of improvement in Glasgow Coma Score (GCS) of both groups and then compared. Primary endpoint will be clinical improvement after 7 days.

Conclusion: The rationale behind which drug of the two - mannitol or hypertonic saline solution (HS) - for treatment of people suffering Traumatic Brain Injury (TBI) to be primary varies considerably and there seems to be no protocol to determine which of these should be preferred. Most of the studies that have been done on the topic conclude that Hypertonic saline (HTS) seems to better suited for lowering Intracranial Pressure (ICP), regardless of its concentration. However, other than its apparent superiority in ICP reduction, it doesn't seem to have any additional benefits, in relation to mortality.
Keywords: Mannitol, Hypertonic Saline, Traumatic Brain Injury, Intracranial Hypertension, Intracranial Pressure

Introduction –

While the etiology of Traumatic Brain Injury may differ, overall it may be explained as damage to the brain by outside force. This includes blunt force injury, stab wound due to penetration o an object into the cranium or a blast wave due to explosion. (1) It may be categorized into 3 types: mild, moderate or severe. The categorization is done considering the help of Glasgow Coma Scale (GCS).(2) Traumatic Brain Injury (TBI) is a huge part in cases of disability and morbidity around the world.(3) The prognosis of TBI is very poor as roughly one third patients suffering from it die, while another one third go through poor recovery and

rehabilitation.(4) Around 1.6 million people suffer head injury in India each year, which results in more than 200,000 deaths. TBI is very common in India, its prevalence being about 9.7 million.(5) Globally, it is estimated that about 64-74 million cases of Traumatic Brain Injury are recorded each year.(6)

A lot of complications are seen because of Traumatic Brain Injury (TBI). Some complications which may be manifested early are: 1) increased Intracranial Pressure (ICP) 2) decreased Cerebral Perfusion Pressure (CPP) which causes ischemia. 3) seizures which may lead to hypoxia in the brain. If the hypoxia continues for 5 or more minutes, the effects may be irreparable. 4) electrolyte imbalance and hypoxemia.(7)

However, the most common outcomes of Traumatic Brain Injury remain Intracranial Hypertension and cerebral oedema. These injuries, whether acute or chronic, which may result in these complications, may be caused due to trauma, stroke, infections, aneurysms, haemorrhage, tumours, etc.(8)

Intracranial Hypertension (IH) can be explained as follows: Intracranial Pressure (ICP) above 20 mm of Hg for more than 5 minutes. This condition worsens prognosis of Traumatic Brain Injury (TBI). (9) If it is not diagnosed early and prompt treatment is not given, it may progress to brain herniation and death.(10) The pressure that is exerted by the contents of the cranium on the dura is known as Intracranial Pressure (ICP).(11) The contents are: the brain which comprises 80% of the contents, cerebrospinal fluid which accounts for 10% of intracranial volume 10% and blood which constitutes the remaining 10%.(12) Normally, the Intracranial Pressure (ICP) should be between 5 to 15 mm of Hg in adults.(13) Cerebral ischemia is caused due to decreased Cerebral perfusion pressure(CPP), which is caused due to increased Intracranial Pressure (ICP). As a compensatory mechanism, blood flow of the cerebrum is increased, further increasing Intracranial Pressure (ICP). And a vicious cycle is formed.(14)

Any abnormal presence of fluid in the cerebrum is termed as cerebral edema.(15) Cerebral edema is recorded in about half of the people with history of Traumatic Brain Injury (TBI).(16) As hypothesized by Monro and Kellie in their Monro-Kellie doctrine, the total of the parts of the cranium, i.e. cerebrum, intravascular component or cerebrospinal fluid (CSF) is always th same.(17) As such, when concentration of any of the constituents rises, the concentration of remaining two has to decrease.(18) Cerebral edema may be caused by increase in one or more components of the cranium.(19)

Management techniques of Intracranial Hypertension range from barbiturate coma, Cerebrospinal fluid (CSF) drainage, decompressive craniectomy and hyperosmolar therapy.(20) Weed and McKibben revolutionized neurosurgery when they established that Hyperosmolar therapy reduces Intracranial Pressure in 1919.(21) Since then, hyperosmolar therapy still remains the standard intervention modality in Intracranial Hypertension fir patients with Traumatic Brain Injury.(22) Hyperosmolar therapy acts by forming an osmotic gradient. This gradient words through he Blood Brain Barrier (BBB) and helps in transporting the fluid accumulated in the brain into the intravascular compartment.(23) An ideal agent should stay within the intravascular component while it draws the fluid out of the brain.(24) The ideal agent used is one which lowers Intracranial Pressure (ICP) while also sustaining the Cerebral Perfusion Pressure (CPP) at the same level.(25) An ideal hyperosmolar agent is non-reactive, non-toxic and should not have any major unwanted effects.(26)

During early era, urea, glycerol and mannitol were used. However, urea and glycerol turned out to be less efficacious. Thus, they are now obsolete.(27) Mannitol is still advocated as the

gold standard for the betterment of the patient suffering from Intracranial Hypertension, despite its multitudes of side effects.(28) Mannitol (usually 20%) is used in dosage of 0.25 to 1 kg every 6 hours. However, dosage of more than 0.5 kg is to be preferred.(29) However it also has many side effects such as electrolyte imbalance and hypotension. Paradoxically, Mannitol may also worsen intracranial edema.(30) Mannitol transports fluid into the intravascular compartment and being a diuretic, it results in diuresis, which may lead to hypovolemia.(31) It may also lead to renal toxicity given the increased serum osmolality.(32) Decreasing efficacy has also been reported with consecutive doses.(33) Due to these side effects, other drugs are being investigated which may have a lower range of side effects.(34)

One of the drugs being considered is Hypertonic Saline. It seems like a good alternative to treat Intracranial Hypertension.(35) Not only is it cheaper, but is also as efficacious as Mannitol.(36) It also has lower Blood Brain Barrier permeability and lesser side effects than Mannitol.(37) The recommended dose is from one-foru mL/kg.(38)

While there have been many studies done to this effect, the results have been inconclusive.(39) The studies have also not reached a consensus about the dosage and concentration of Hypertonic Saline which would be most beneficial to the patient. This necessitates further research.(38)

The authors have conducted a Blind Prospective Interventional Cross-sectional Randomized Study. It was considered as the appropriate study plan as it gave a chance to be able to compare the efficacy of both the drugs simultaneously. The rationale behind selecting this system was to be easily able to compare both the drugs in similar environment which would help reducing any external variables.

The patients were analysed on the basis of the rates of improvement in their Glasgow Coma Score (GCS). Glasgow Coma Scale (GCS) assesses patients based on 3 components: ocular response, speech and motor response.(40) The ocular response is scored from 1 to 4 based on whether the patient is opening his eyes, and whether any stimulus is required for it. The verbal responses are scored on whether the patient can speak, whether what he is saying is in context of the question that has been asked and whether his speech is comprehensible. It is scored from 1 to 5 while the motor responses are scored from 1 to 6, based on whether the patient has enough control over his muscles voluntarily or in pain.(41)

Glasgow Coma Scale is assessed as follows(42):

Category	Response	Score
Eye opening	Blinking and spontaneous opening of eyes	4
	Eyes open when give a verbal command	3
	Eyes open when given a painful stimulus	2
	Eyes remain shut	1
Speech	Patient is well-oriented	5
	Patient is confused but	4

	able to answer all questions appropriately	
	Words are comprehensible but response is not appropriate to the question asked	3
	Speech cannot be understood	2
	Patient is unable to speak	1
Motor response	Patients moves in response to command	6
	Patient localizes to pain	5
	Patient moves away from pain	4
	Abnormal flexion	3
	Abnormal extension	2
	Patient cannot move eben on stimulus of any king	1

Table 1: Glasgow Coma Scale and Scoring

Glasgow Coma Score helps to categorize Traumatic Brain Injury into 3 types(43):

Glasgow Coma Score	Grade of Traumatic Brain Injury
13-15	Mild (Concussion)
9-12	Moderate
Less than 8	Severe

Table 2: How Glasgow coma scoring is used to classify Traumatic Brain Injury

Objectives - The reason for conducting this study is to appreciate the difference in the effects of using mannitol and hypertonic saline (HTS) in similar doses to decrease Intracranial Pressure (ICP) in patients who were admitted due to moderate or severe traumatic brain injury (TBI).

Methodology –

Type of Study – Simple (Computer generated) randomized trial

Study Design – Blind Prospective Interventional Cross-sectional Randomized Study

Setting – The trial will be conducted in Acharya Vinoba Bhave Rural Hospital, Sawangi (Meghe), Wardha.

The conducted study was a prospective study, which will take place in the tertiary care hospital affiliated to the university for 2 months on 130 patients. The selected participants of the study were distributed into 2 groups with 65 patients in each group.

Participants – All patients of moderate to severe Traumatic Brain Injury (TBI), i.e. patients who had Glasgow Coma Score of less than 13 during admission in the hospital over the course of 2 months of the study will be included. Patients who were only treated with one interventional agent, either Mannitol or Hypertonic Saline, will be included. Pediatrics patients, that is, those who were below 16 years of age will be excluded. Patients with post traumatic subarachnoid hemorrhage were included. All operated and medically managed patients of moderate to severe Traumatic Brain Injury (TBI) will be included for the study. Patients with renal failure will be excluded from the study.

Variables – The independent variable (grouping variable) is the drug – Mannitol or Hypertonic Saline (3%), while the dependent variable is the rate of reduction of Intracranial Pressure (ICP).

Data Collection – The required information regarding the patients will be acquired from the patient records at the hospital. Intracranial Pressure (ICP) measurement being a very invasive procedure, the outcome will be analysed on the basis of Glasgow Coma Scale (GCS).

Bias – Since the data will be collected from the patient records at the hospital, Respondent bias, Question–order bias and Leading Questions and wording bias will be minimum. The study will be re-evaluated continually to eliminate Confirmation bias.

Study Size – $$n = \frac{Z_{\alpha/2}^2 \times P \times (1-P)}{d^2}$$

Where;

$Z_{\alpha/2}$ = level of significance at 5% i.e. 95%

Confidence interval =1.96

P = Prevalence of TBI = 0.9% = 0.09

d = Desired error of margin =7%

$$n = \frac{1.96^2 \times 0.09 \times (1-0.09)}{0.07^2}$$

$$= 64.20$$

n = 65 patients in each group

Quantitative Variables – Patients will be divided into subgroups, based on how severe the Traumatic Brain Injury (TBI) is. The criteria to divide them will be Glasgow Coma Score (GCS). Traumatic Brain Injury is divided into 3 types on the basis of Glasgow Coma Scale(43):

Glasgow Coma Score	Grade of Traumatic Brain Injury
13-15	Mild (Concussion)
9-12	Moderate
Less than 8	Severe

Table 3: Glasgow Coma scale and its usage for classification of Traumatic Brain Injury

Statistical analysis – Statistical analysis will be done by using descriptive and inferential statistics using Student's unpaired t test and the software using the analysis will be SPSS 24.0 version and GraphPad Prism 7.0 version and $p<0.05$ is considered as level of significance.

Methods – Patients will be randomized into 2 statistically comparable groups. Group A and Group B will be treated with the standard dose of mannitol and Hypertonic Saline (3%) and clinical outcome will be noted for the next 7 days. Primary endpoint will be clinical improvement after 7 days. Side effects, like electrolyte imbalance and hypotension due to Mannitol, will be monitored. If during routine Kidney Function tests, sodium level in the serum is found to be above 150 mEq/L, administration of Hypertonic Saline will be stopped.

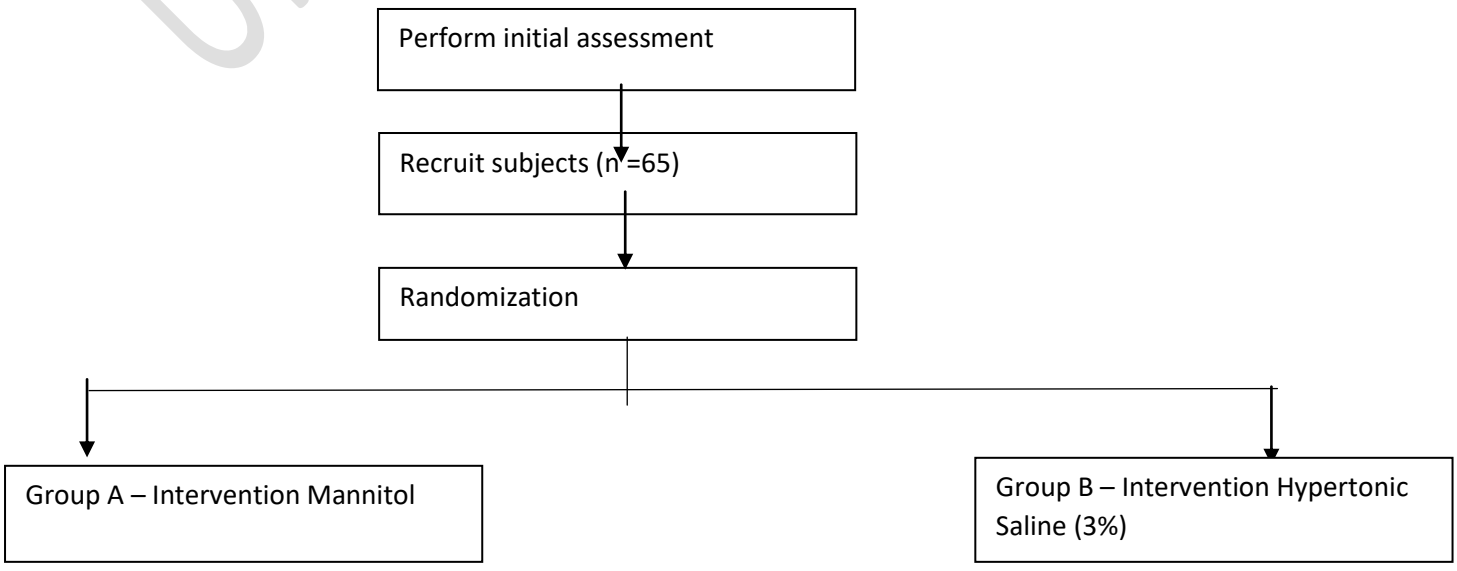
Relatives of the patient gave their informed consent after they had been appropriately told about the study. Before conducting the study, an approval letter was received from the ethics committee of the institution. Glasgow Coma Score of patients will be periodically checked.

Patients will undergo routine Kidney Function Tests to monitor their Serum Sodium and Serum Potassium levels. This will be done considering the side effects of both the drugs, as both the drugs are known to cause electrolyte imbalance.

Expected Outcomes:

Participants:

Fig. 1. Flow diagram of study procedure



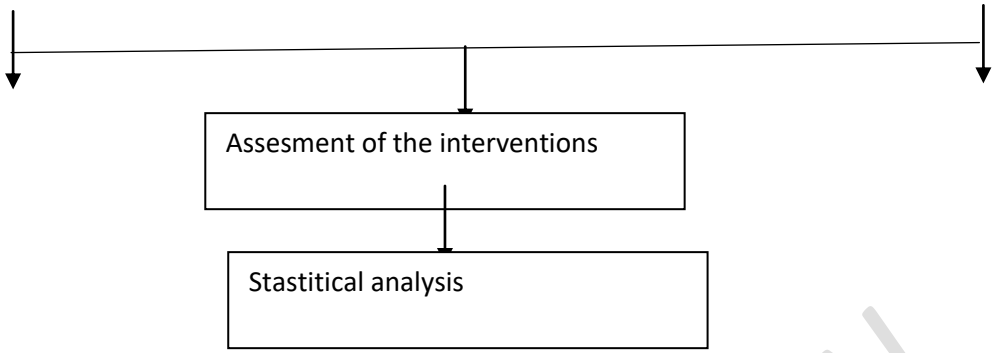


Fig. 2. Schedule of enrolment and initial assessment of GCS

Date of Admission	
GCS (after interventions) :	
On arrival	
After 12 hours	
After 24 hours	
After 48 hours	
After 72 hours	

Descriptive Data: All patients of moderate to severe Traumatic Brain Injury (TBI), i.e., patiets who were reported with Glasgow Coma Score of less than 13, admitted in the hospital over the course of 2 months of the study will be included. The required information will be collected from the patient records at the hospital.

Outcome Data: The outcome will be decided by the rate of improvement in Glasgow Coma Score (GCS) for both interventions at the end of 7 days.

Discussion:

Key Results: This trial will study the difference in effects of both the drugs in reducing Intracranial Pressure (ICP) in patients who had been admitted to the hospital to be trated for moderate or severe Traumatic Brain Injury (TBI) and compare the same. The two drugs will be compared on the basis of Glasgow Coma Score recorded during discharge, difference between Glasgow Coma Score recorded at admission and discharge, Rate of improvement in Glasgow Coma Score per day and duration of the stay of the patient. Glasgow Coma when patient is discharged is taken into account to ascertain that all patients in the two groups reach the appropriate GCS on discharge, and if not, which of the two groups was unable to ascertain the appropriate target. Difference between Glasgow Coma Score will be calculated so as to check whether the drug is effective and the patient is approving appropriately or not, and to compare the two drugs for the same. The rate of improvement in Glasgow Coma Scale will be calculated by the difference in GCS on admission and GCS on the day of discharge with respect to the number of days the patient was admitted in the hospital. This parameter was decided as it will lead us in better understanding of the efficacy, and whether a drug is

superior in improving the GCS faster. The results, if conclusive, will help us provide a better guideline over which drug should be used in emergencies. Duration of stay in the hospital is also a very important factor to be taken into account as the reasons for analysing this were dual. Not only would it mean that the drug which resulted in a shorter hospital stay is more efficacious, it would also imply that it proves beneficial for the patient with regards to his expenses and his comfort.(44-49)

Drug related complications like electrolyte imbalance and renal failure due to Mannitol and increased serum Sodium level with use of Hypertonic Saline will be monitored.

Limitations: Intracranial Pressure (ICP) measurement is a very invasive procedure, therefore cannot be used for a study where the patient need to be evaluated periodically.

Interpretation: It has been very difficult to compare hypertonic saline (HTS) solution with mannitol because of the range in concentrations available. Recent studies suggest that Hypertonic Saline (HTS) reduces Intracranial Pressure (ICP) burden and improves prognosis, compared to Mannitol, which has many side effects including worsening of cerebral edema. The use of either drug in patients who are admitted for Traumatic Brain Injury (TBI) varies considerably and there seems to be no protocol to determine which of these should be preferred. The majority of existing data on the relevant topic imply Hypertonic Saline (HTS) to be more efficacious in lowering Intracranial pressure (ICP) and Intracranial Hypertension (IH), regardless of its concentration. However, other than its apparent superiority in ICP reduction, it doesn't seem to have any additional benefits, in relation to mortality.

Generalisability: This study will allow us to improve the treatment in all neurocritical conditions, rather than just Traumatic Brain Injury (TBI). Intracranial Hypertension is a dangerous condition. The Intracranial Pressure could be found to high because of any of the intracerebral constituents, which are brain volume, blood volume and CSF. Thus, the etiology of Intracranial Hypertension can be categorized based on which of the component is raised:

Brain volume increases due to trauma, ischemia, hyperammonaemia, Uremic encephalopathy and Hyponatremia causing cerebral edema.

Cerebrospinal fluid (CSF) can be raised either due to its increased production or decreased reabsorption. Increased production of Cerebrospinal fluid (CSF) can be idiopathic or due to choroid plexus tumor. Obstructive hydrocephalus and Meningeal inflammation or granulomas may, on the other hand, be caused due to decreased reabsorption of Cerebrospinal fluid (CSF).

Blood volume may be raised due to either increase in blood flow to the cerebrum or stasis in the veins of the brain. Blood flow of the brain may be increased in conditions such as hypercarbia or an aneurysm. While venous stasis may be a result of venous sinus thrombosis or increased central venous pressure.

Miscellaneous causes be 1) idiopathic such as benign intracranial hypertension. 2) congenital which may be due to skull deformities such as craniosynostosis. 3) Hypervitaminosis A and Tetracycline use.

Intracranial Hypertension (ICH) is treated by Osmotherapy, regardless of the etiology. The result of this study will greatly affect the prophylaxis in all these conditions.

COMPETING INTERESTS DISCLAIMER:

Authors have declared that no competing interests exist. The products used for this research are commonly and predominantly use products in our area of research and country. There is absolutely no conflict of interest between the authors and producers of the products because we do not intend to use these products as an avenue for any litigation but for the advancement of knowledge. Also, the research was not funded by the producing company rather it was funded by personal efforts of the authors.

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