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Compare the efficacy of hypertonic saline vs mannitol as an anti-edema measure, in cases of head injury

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Background: To study the efficacy and safety of 3% hypertonic saline and compare with 20% mannitol in the management of moderate to severe head injury. **Material and Methods:** Group A (patients treated with Mannitol) n=30, Group B (patients treated with 3% hypertonic saline) n=30. Intervention protocol Dose of Mannitol 20% 2ml/Kg infused over 20 minutes 6 or 8 hourly for the group A. Group B infused with 3% 2ml/Kg Hypertonic Saline over 20 minutes. Safety and efficacy compared. **Results:** There was no significant difference in mortality. The duration of coma hours was also not very different. There was no difference in the neurological outcomes of both groups. No significant untoward complications observed in both the groups which were found to be related to the drug. hypertonic saline (3%) therapy in case of moderate to severe head injury is found to be as safe and as efficacious as mannitol. No significant hypernatremia is seen in 97% of our patients of hypertonic saline (3%) group. **Conclusion:** In our comparative prospective study, it can be concluded that the efficiency of 20% Mannitol and 3% Hypertonic Saline for the treatment of cerebral edema in patients with moderate to severe head injury is almost equal.

Keywords: Hypertonic Saline, Mannitol, Head Injury, Traumatic Brain Injury (TBI), Intracranial Injury

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Introduction

Traumatic brain injury (TBI), also known as intracranial injury, occurs when an external force injures the brain. TBI can be classified based on severity, the mechanism (closed or penetrating head injury), or other features (e.g., occurring in a specific location or over a widespread area).Brain trauma occurs as a consequence of a sudden acceleration or deceleration within the cranium or by a complex combination of both movement and sudden impact. In addition to the damage caused at the moment of injury, a variety of events in the minutes to days following the injury may result in secondary injury.

These processes include alterations in cerebral blood flow and the pressure within the skull. Depending on the injury, treatment required may be minimal or may include interventions such as medications, emergency surgery, or surgery years later. In medical interventions, Mannitol and 3% Hypertonic Salineare used. Use of Hypertonic saline as antiedema measure for treating cerebral edema and has been employed since 1960. Urea, glycerol, mannitol were used in the treatment in early years but urea, glycerol was abandoned because of its low efficacy and patients side effects [1].

Mannitol: Mannitol is a type of sugar alcohol that is also used as a medication. As a medication, it is used to decrease pressure in the eyes, as in glaucoma, and to lower increased intracranial pressure. Medically, it is given by injection. Effects typically begin within 15 minutes and last up to 8 hours. Common side effects from medical use include electrolyte imbalance and dehydration. Other serious side effects may include worsening heart failure and nephrotoxicity [1-3].

Saline: Saline, also known as saline solution, is a mixture of sodium chloride in water and has a number of uses in medicine. Large amounts may result in fluid overload, swelling, acidosis, and high blood sodium. Saline is in the crystalloid family of medications. Saline has a pH of 5.5 making it highly acidic [1-4].

Our aim in this study is to compare the efficacy of Hypertonic Saline vs Mannitol as an anti-edema measure, in cases of moderate to severe head injury. Side effects such as rebound edema, hypovolemia, and nephrotoxicity have to lead to the search for new agents one of them being hypertonic saline. So this prospective study is conducted in our Department to know the efficacy and safety of hypertonic saline as compared to Mannitol.

Materials and Methods

Study design: A comparative prospective study

Setting: Department of Surgery, Hamidia Hospital, Bhopal, Madhya Pradesh, India

Inclusion criteria: 60 patients admitted to the Department of Surgery with moderate to severe head injury over 18 years of age from March 2017 to March 2018, whose attendant also gave consent.

Exclusion criteria: Patients with: Age<18 years

Groups and method of randomization

Group A (patients treated with Mannitol) n=30

Group B (patients treated with 3% hypertonic saline) n=30.

Intervention protocol: Dose of Mannitol 20% 2ml/Kg infused over 20 minutes 6 or 8 hourly for the group A. Group B infused with 3% 2ml/Kg Hypertonic Saline over 20 minutes.
01. **creatinine:** First day and 4th day.

Serum electrolytes: Initial five days.

MAP (Mean Arterial Pressure): As per the recordings of the BP pre-drug and post-drug administration for five consecutive days.

Duration of Coma hours: Measured during the period of hospitalization

Ethical approval: Taken

Evaluation of the response to intervention

Statistical Analysis: After getting the required information, the collected data were coded, tabulated, and analyzed. The various statistical techniques i.e. the mean, standard deviation, and test of significance (t-test and chi-squaretest) were used for drawing valid conclusions. Statistical analysis was done using the student t-test.

SPSS 13.0 software was used to calculate the p-value. $P<0.05$ was taken as statistically A descriptive analysis was done on all variables to obtain a frequency distribution. The mean + SD and ranges were calculated for quantitative variables. Continuous variables were compared by the Student t-test. Proportions were analyzed with the chi-square test.

Results

Table-1: Management.

Management	No. of cases in the mannitol group (group a)	No of cases in the hypertonic saline group (Group B)
Operative	13(43.3%)	16 (53.3%)
Conservative	17 (56.6%)	14 (46.6%)
Total	30	30

In the Mannitol group 43.3% operated and 56.6% managed conservatively and in the hypertonic saline group, 53.3% operated and 46.6% managed conservatively.

Table-2: Outcome of the patient in the mannitol and hypertonic saline group.

Outcome	Mannitol Group (Group A)	HTS Group (Group B)
Improved	24(80%)	22(73.3%)
Death	6(20%)	8(26.6%)
Total	30	30

Table-3: Mean arterial pressure and GCS of patients in the mannitol group.

Day	Pre-drug MAP	Pre-drug GCS	Post-drug MAP	Post-drug GCS
1	92.84	9	88.5	9
2	90.01	8	86.5	8
3	87.65	9	84	9
4	88.67	10	87.48	10
5	90.21	12	89.40	12

MAP measurement pre-drug (mannitol) and a half-hour after mannitol which was significantly decreased in initially 3 days and later its effect decreases

Table-4: Mean arterial pressure and GCS in patients of the hypertonic saline group

Day	Pre-drug MAP	Pre-drug GCS	Post-drug MAP	Post-drug GCS
1	90.86	8	89.5	8
2	89.94	9	88.68	9
3	90.01	9	88.72	9
4	88.52	10	87.42	10
5	89.20	12	88.41	12

Table-5: GCS score of the patients in the mannitol group (group A).

GCS	ON Admission	Improved	Death
3-5 (very severe head injury)	8	1	7
6-8(severe head injury)	8	8	0
9-12 (moderate-severe head injury)	14	14	0

Table-6: GCS score of the patients in the hypertonic saline group (Group B).

GCS	ON Admission	Improved	Death
3-5	5	1	4
6-8	12	9	3
9-12	13	13	0

A maximum number of patients wherein the younger age group in both groups. The male and female ratio was almost equal in both the groups, in Mannitol group 5:1 and in hypertonic saline group 7:3. In the Mannitol group 43.3% operated and 56.6% managed conservatively and in the hypertonic saline group, 53.3% operated and 46.6% managed conservatively. The percentage of death was almost equal in both groups.

The duration of the coma was also almost similar in both the groups. Serum Na + levels were on the lower side in both groups but lower levels were seen in the mannitol group (1 patient has hypernatremia in 3% hypertonic saline group). Changes in MAP after hypertonic saline was relatively less but constant throughout in initial 5 days. Mortality was very high in very severe head injury patients and this was almost the same in both the groups.

Discussion

In the present study, there were 60 patients of moderate to severe head injury. these patients were randomized into 2 groups, 1 group receiving Mannitol [group A] and other group receiving hypertonic saline 3% [group B]. Most of the patients in both groups are in the younger age group. The mean age in the mannitol group was 39 years and in the hypertonic saline group was 37 years. In the present study male-female ratio is almost equal in both the group which is similar to the study conducted by Piyush Upadhyay et al[1].

Upadhyay P et al did a randomized comparative study on the role of hypertonic saline and mannitol in the management of raised intracranial pressure in children. They did in the Pediatric intensive care unit (PICU) in a tertiary care hospital on 200 patients with raised intracranial pressure. The decrease in MAP was highly significant ($P<0.001$) at 0 h in males 0,6 h in females, and moderately significant at 12,36 h in females and significant($P<0.05$) at 6,24,42 h in males of Group B.

Decrease in coma hours was a highly significant finding ($P<0.001$) in Group B. In Group B, serum sodium and chloride increased significantly but remained within acceptable limits. There was no difference between osmolality and mortality (fisher Z).So it was concluded Mannitol has several side effects, 3% hypertonic saline is a safe and effective

Alternative in managing cerebral edema. In the present study, the duration of coma hours is equal in both the group as the observation shows. No significant difference. The mean value of the duration of the coma for the group treated with Mannitol was 73.6±38.8 hours whereas for the group treated with hypertonic saline was 77.25±33.8. Piyush Upadhyay et al found a decrease in coma hours was highly significant in the group treated with hypertonic saline which is contrary to the present study [1].

In the present study, there is no difference observed for the comparison of the serum electrolyte level. The investigations were noted for the sodium level in the patient treated with Mannitol and 3 % hypertonic saline from day1 to day 5. The observation between the reading of the group shows that sodium levels treated with Mannitol were slightly declining with succeeding days whereas no significant changes in patients treated with hypertonic saline as compared to the Mannitol group.

In one out of 30 patients hypertonic saline group had to be stopped due to hypernatremia on the 5th day. hypernatremia is not found as a regular feature in the patients treated with hypertonic saline. In Piyush Upadhaya et al study in GSVM, the group treated with hypertonic saline serum sodium increases significantly but remains within the acceptable limit.

In the present study, the group was also compared for mean arterial pressure in which the group treated with Mannitol and 3 % hypertonic saline were recorded with pre and post-drug mean arterial pressure for both the group same for consecutive 5 days but in the study of Piyush Upadhaya et al decrease in mean arterial pressure was highly significant at 6, 24, 42 hours in males and 0,6 hours in females and moderately significant at 12, 36 hours in females and significant at 6,24,42 hours in groups treated with hypertonic saline as compared to Mannitol group [2].

Ziai WC et al used hypertonic saline as first-line therapy for cerebral edema. Their article highlights the experimental and clinical data, controversies, and postulated mechanisms surrounding osmotherapy with hypertonic saline (HS) solutions in the neurocritical care arena and builds on previous reviews on the subject. Special attention is focused on HS therapy on commonly encountered clinical paradigms of acute brain injury including Traumatic brain injury (TBI), post-operative "retraction edema", intracranial hemorrhage (ICH), tumor-associated cerebral edema, and ischemia associated with ischemic stroke [3]. Kheirbek T studied hypertonic saline and Mendelow AD et al studied the effect of mannitol on cerebral blood flow and cerebral perfusion pressure in human head injury. The aim of both studies was to determine the effect of mannitol and hypertonic saline on ICP, cerebral perfusion pressure (CPP), and cerebral blood flow (CBF) in patients with a severe head injury, and to discover if these effects differed in different types of injury. Measurements of CPP, ICP, and CBF were made in 55 patients with a severe head injury. In general, the resting level of CBF was higher in patients with diffuse injury (mean 50.2 ml/100 gm/min) than in those with focal injury (mean 39.8 ml/100 gm/min). Mannitol consistently reduced ICP and increased CPP and CBF by 10 to 20 minutes after infusion [4]. Wakai A et al used mannitol for acute traumatic brain injury. They saw that mannitol is sometimes effective in reversing acute brain swelling, but its effectiveness in the ongoing management of severe head injury remains unclear. There is evidence that, in prolonged dosage, mannitol may pass from the blood into the brain, where it might cause increased intracranial pressure. In the acute management of comatose patients with a severe head injury, the administration of high dose mannitol resulted in reduced mortality (RR= 0.56; 95% CI 0.39 to 0.79) and reduced death and severe disability (RR= 0.58; 95% CI 0.47 to 0.72) when compared with conventional dose mannitol. So it was concluded that high dose mannitol may be preferable to conventional dose mannitol in the acute management of comatose patients with a severe head injury. Mannitol therapy for raised ICP may have a beneficial effect on mortality when compared to pentobarbital treatment but may have a detrimental effect on mortality when compared to hypertonic saline [5]. Smith HP et al did a comparison of mannitol regimens in patients with severe head injury undergoing intracranial monitoring on eighty patients sustaining head injuries and presenting with Glasgow Coma Scale scores of 8 or less were entered into a prospective randomized study to assess the benefit of intracranial pressure (ICP) monitoring with two regimens of mannitol administration. Group, I was treated with mannitol for ICP elevations greater than 25 mm Hg, while Group II received empirical mannitol therapy irrespective of ICP readings.

No statistically significant differences in mortality rate or neurological outcome were demonstrated between the two groups. These results are comparable to those of several published series of head-injured patients receiving similar treatment [7]. Toung TJ, Bhardwaj A et al studied the effect of mannitol and hypertonic saline on changes in lung and brain water following experimental stroke whereas two years later they studied the effects of hypertonic saline and saw that it attenuates water content in the brain and extracerebral organs. It was concluded that the use of 23.4% hypertonic saline with children admitted for severe traumatic brain injury is associated with a statistically significant decrease in intracranial pressure within 1 hour of use [8]. Boas WW et al studied hydroelectrolytic balance and cerebral relaxation with hypertonic isoncotic saline versus mannitol (20%) during elective neuroanesthesia. A statistically significant difference in cerebral relaxation between both groups was not observed. Although several changes in electrolyte levels and acid-base balance with mannitol or HIS reached statistical significance only the reduction in plasma sodium 30 minutes after infusion of mannitol. The mannitol (20%) group had a significantly greater diuresis at both times studied compared with the HIS group. A single dose of hypertonic isoncotic saline solution [7.2% NaCl/6% HES (200/0.5)] and mannitol (20%) with equivalent osmolar loads was effective and safe in producing cerebral relaxation during elective neurosurgical procedures under general anesthesia [9]. A similar study was done by Raghava A et al who did a comparison of equimolar concentrations of hypertonic saline and mannitol for the intraoperative lax brain in patients undergoing craniotomy. Brain relaxation was comparable in two groups and there was no significant difference (P = 0.633). Compared with mannitol, hypertonic saline caused an increase in the serum osmolality at 120 min (P = 0.008) and in serum sodium at 120 min (P = 0.001). Urine output was higher with mannitol than hypertonic saline (P = 0.001).So it was concluded that3% hypertonic saline and 20% mannitol are equally effective for brain relaxation in elective supratentorial tumor surgery and compared with mannitol, hypertonic saline was associated with a less diuretic effect. In the present study, No increase in serum creatinine levels in both groups. Nephrotoxicity is not significant in both the groups if the patient is kept hydrated. There was also no significant difference found in serum creatinine levels in the study conducted by Nicholas et al [10].

A prospective, randomized, double-blind study was done by Malik Za et al to compare the effects of equimolar solutions of 3% hypertonic saline and 20% mannitol on the reduction of brain-bulk during elective craniotomy for supratentorial brain tumor resection. Brain relaxation conditions in the HTS group (relaxed/satisfactory/firm/bulging, n = 28/20/5/3) were better than those observed in the M group (relaxed/satisfactory/firm/bulging, n = 17/21/11/9). The levels of serum sodium were higher in the HTS group (P< 0.001). The average urine output was higher in the M group (5.50 ± 0.75 L) than in the HTS group (4.38 ± 0.72 L) (P< 0.005). They concluded that HTS provided better brain relaxation than mannitol during elective supratentorial brain tumor surgery, without affecting ICU and hospital stay [11]. In the present study, 43% of patients were operated and 56.6% of patients were kept on the conservative line of management in the Mannitol group. And 53.3% of patients were operated and 46.6% of patients were kept on conservative management in the hypertonic saline group. almost equal in both groups. In Nicholas salcellaridis et al study in KAT hospital in Attica, Greece.55.1% of patients were operated and 44.82% of patients were managed conservatively. In the present study there is no significant difference found in the blood investigation of patients of both the group and in Nicholas Sacellaridis et al. study blood investigations were almost most equal in both the group [12].

Limitation

01. Small sample size

02. Chances of bias

03. Single-center trial

Conclusion

In the current comparative prospective study, it can be concluded that the efficiency of 20% Mannitol and 3% Hypertonic Saline for the treatment of cerebral edema in patients with moderate to severe head injury is almost equal. There was no significant difference in mortality. The duration of coma hours was also not very different. There was no difference in the neurological outcomes of both groups. No significant untoward complications observed in both the groups which were found to be related to the drug. hypertonic saline (3%) therapy in case of moderate to severe head injury is found to be as safe and as efficacious as mannitol. No significant hypernatremia is seen in 97% of our patients of

Hypertonic saline (3%) group.

What does the study add to the existing knowledge?

3% hypertonic saline and 20% mannitol are equally effective for brain relaxation in head injury and compared with mannitol, hypertonic saline was associated with a less diuretic effect. In the present study, No increase in serum creatinine levels in both groups. Nephrotoxicity is not significant in both the groups if the patient is kept hydrated.

Author's contribution

Dr. A.K. Chaurasia: Concept and discussion

Dr. Rajneesh Gour: Concept and Data collection

Dr. Deepti Dhodi: Data Collection

Prof. Dr. M.C. Songra: Concept and Guidance

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