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Efficacy of different hypertonic solutes in the treatment of refractory intracranial hypertension in severe head injury patients: A comparative study of 2ml/kg 7.5% hypertonic saline and 2ml/kg 20% mannitol

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Abstract: A prospective, randomized study to evaluate the clinical benefit of increasing the osmotic load of the hypertonic solution administered for the treatment of refractory intracranial hypertension episodes in patients with severe head injury. 25 patients with severe head injury and persistent coma, admitted in a Neurocritical Care Unit of a Tertiary Care Hospital, who required infusions of osmotic agents to treat episodes of intracranial hypertension resistant to well defined standard modes of therapy were randomly allocated to one of the two groups to receive isovolume infusions of either 7.5% hypertonic saline solution; HS [2400 mOsm/kg H_2O] or 20% mannitol [1160 mOsm/kg of H_2O] given 2ml/kg of either solution, i.e. 331.5 +/- 35.4 mOsm of hypertonic saline or 174.2 +/- 18 mOsm of mannitol per infusion. The variables recorded in the study were the duration and number of episodes of intracranial hypertension per day during the study period, which was stopped after the last episode of intracranial hypertension was recorded from intracranial pressure recording or after the allocated treatment failure. Patients of HS group were monitored for 7 +/- 6 days and those in the mannitol group for 8 +/- 5 days [p=NS]. The rate of failure for each treatment was also evaluated which was defined as the persistence of intracranial hypertension despite the two successive infusions of the same osmotic agent. The mean number of osmotic solute infusions was 3.4 +/- 4.5 in the HS group and 3.8 +/- 5.1 in mannitol group p=NS]. The mean number [7.1+/-2.9 vs. 14.6+/-3.4] of episodes of intracranial hypertension per day and the duration of such episode [62.6+/-28.1 vs. 93.4+/-37.2 min] was also significantly lower in the HS group [p<0.05]. The numbers of treatment failures were significantly lower in HS group: 1 out of 14 patients vs. 6 out of 11 patients [p<0.01]. In this study we have found that in patients with severe head injury requiring treatment with hypertonic solute for refractory intracranial hypertension, 2ml/kg body weight of 7.5% HS [356 +/- 14 mOsm] was more effective than giving 2ml/kg 20% mannitol [178 +/- 11mOsm]. Within the limitations of present study, the collected data suggest that giving 2ml/kg HS solution is an effective and safe initial treatment for intracranial hypertension episodes in head injury patients when there is indication of osmotherapy.

Keywords: Intracranial Hypertension, Mannitol, Hypertonic Saline, Head Injury

INTRODUCTION

Infusion of Hyperosmolar solutes is one of the treatments that is currently recognized for intracranial hypertension [ICH] after severe head injury, and 20% mannitol is the reference solute[1,2,3]. However it is not free from adverse effects particularly after repeated administration, like acute renal failure[4,5,6], hypovolemia [4,6,7], and rebound increase in intracranial pressure [ICP][4,8,9,10] Hypertonic saline has attenuated ICH in a number of clinical trials[11,12,13,14]. First proposed for the treatment of hemorrhagic shock, 7.5% hypertonic saline [HS] it is now one of the established modalities of treatment for ICH[3,15,16,17]. Experimental trials comparing these two ways of treating ICH are not conclusive[18,19,20], although some trials favour the use of HS[11]. HS is used over quite a long period in our centre alternatively with mannitol. The observation of a huge number of failures with mannitol, whereas HS appeared to remain effective, has encouraged us to evaluate more precisely the relative efficacy of the two solutes. Hence, in the following section we report the results of a prospective, randomized clinical study, with an objective to compare the efficacy of

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mannitol and HS, perfused at the same volume, in patients with refractory ICH episodes following severe head injury.

MATERIALS AND METHODS

This is a single centre study, performed at a neurocritical care unit of a tertiary care multispecialty hospital. After prior approval of the study protocol from the ethics committee, written and informed consents were obtained from the closest relatives of each of the patients, and head injury patients were included if they had persistent coma requiring ICP monitoring and infusion of an osmotic agent to correct refractory episodes of ICP that are resistant to standard modes of therapy. ICH was considered when it persisted despite deep sedation, optimal hemodynamic status, and, in some patients, drainage of cerebrospinal fluid.

Patients with severe injury who were admitted to the neurocritical care unit submitted to a written standardized protocol. Hence all the patients of this study were subjected to same therapy expect the solute chosen for osmotherapy. After initial full resuscitation, and evaluation of neurological status in the trauma unit all the patients with GCS </= 8 were intubated and ventilated mechanically with a sedative regimen comprising of midazolam and fentanyl and transferred to neurocritical care unit. The targets of mechanical ventilation were to keep blood oxygen saturation >95% and to keep $PaCO_2$ between 35 to 38 mm Hg. Insulin was administered whenever capillary blood sugar exceeded 10 mmol/l. Body temperature was monitored and kept in the range of 37^0 +/- 1^0C.

Patient was positioned with 20^0 head elevation. All the routine monitors e.g. pulse oxymetry, ECG, non invasive blood pressure. Central venous cannula, arterial catheters were inserted, haemodyamics were stabilized, then a catheter was inserted for measurement of ICP on the most pathologic side: usually an intraventricular catheter [IVC] whenever possible, else an intraparenchymal catheter [Camino Catheter System, Camino Laboratories; San Diego, CA]. CT scan was performed on admission, at 24 hours, and then at least once a week.

Aim of the therapy was to maintain ICP<25 mm Hg and a cerebral perfusion pressure [CPP] >70 mm Hg. When these ICP values were exceeded for more than 5 minutes [excluding noxious stimulation], first the CT scans were evaluated for possible neurosurgical complications, and then subjected to a multistage treatment. First if the patient was on IVC, the catheter was opened to remove CSF, the level at which catheter was placed, was 20 mm Hg above tragus of ear. The catheter was closed as soon as CSF stopped flowing. Then any fall in CPP after a fall in mean arterial pressure was corrected by volume infusion and/or vasopressor support. In case of hypovolemia [CVP<10 mm Hg], volume infusion was prescribed with hydroxyethyl starch or 0.9% saline. Once hypovolemia was corrected, vasopressor treatment, if necessary, began with dopamine [maximum upto15mcg/kg/min] and/or norepinephrine [0.1-1 mcg/kg/min]. Mean arterial pressure was increased to a maximum of 110 mm Hg. If sedation appeared to be insufficient, the dose of sedatives was increased. When the ICP was increased as a result of tracheal suctioning the patient was paralysed. Hyperventilation was indicated when ICH was not controlled by correcting mean arterial pressure and deepening sedation, when $SjVO_2$ was >75%, hyperventilation was initiated to restore SjVO2 between 55% to 75%. 5 patients in HS group and 2 patients in Mannitol group were monitored with jugular bulb oxymetry. 1 patient in each group was subjected to hyperventilation.

Study Protocol: When even after the above mentioned treatments, ICP was still remaining >25 mm Hg for at least 5 minutes without any noxious stimulation, the episode was considered *refractory* and osmotherapy was prescribed with either 20% mannitol [1160 mOsm/kg/H_2O] or 7.5% hypertonic saline [2400 mOsm/kg/H_2O]. The volume of infusion was same for both type of medications, 2ml/kg body weight in 20 minutes. Thus the patients received either 2.3 mOsm/kg body weight of mannitol or 4.8 mOsm/kg body weight of HS. The aim was to decrease ICP <25 mmHg and CPP >70 mm Hg. In case of failure to achieve the targeted goals after first infusion a second infusion was given, 10 minutes after the end of first infusion. Treatment failure was defined as inability to decrease ICP <35 mm Hg and to increase CPP >70 mm Hg with two consecutive infusions of same osmotic solutions. In such cases the protocol was stopped and the patients were followed up for a period of 60 days neurologic status or for mortality.

The data collected from the patients are as follows: age, body weight, GCS at admission, Injury Severity Score and Simplified Acute Physiology Score. Natremic status, osmolality, haematrorit, number of injections of

desmopresssin acetate were collected from each patients chart. Water and sodium input and output were assessed daily. Daily sodium intake was calculated as the sum of its parts in crystalloid and colloid solutions. Urine specimens were collected every 24 hours, urine volume was recorded, and urine sodium was analyzed for sodium and water balance. Heart rate, arterial blood pressure measured invasively, was continuously recorded [Hewlett Packard, M1205 H]. The infusion rate of dopamine and norepinephrine was noted every day at 9 a.m. and 9 p.m. For patients with IVC, each opening of catheter was regarded as one episode of ICH. Charts were prepared after gathering data every 5 minutes for each 24 hour period. The number and duration of ICH episodes and decreases of CPP were noted from these charts and analyzed. The number of times of catheter opening and amount of cerebrospinal fluid drained were collected from nurse's monitoring forms. IVC was opened when necessary, as per written protocols, by critical care residents.

The mean variables evaluated in this prospective comparative study were the daily number and duration of ICH episodes during the study period, which was stopped after the last ICH was recorded from ICP monitoring. The failure rate of each treatment was also evaluated.

Statistical analysis: The results obtained from the study are presented in the following section in a tabulated manner. The results are expressed in mean +/- SD. Comparison between groups were performed with the Kruskal-Wallis one way ANOVA by ranks or Fisher's exact test for small samples with a 5% risk. Mann-Whitney-Wilcoxon tests were performed when normality tests failed. [Graph Pad InStat version 3.05, Graph Pad Software, SanDiego, CA]

Table 1: Demographic data

Parameter	Mannitol group n=11]	Hypertonic Saline group [n=14]	P value
Age [years]	31.4+/-14.6	35.1+/-17.7	0.57
Weight [kg]	74.2+/-6.9	69+/-11.5	0.18
Males: Females	4:7	6:14	

RESULTS

Eleven patients were randomly allocated in mannitol group and 14 patients were allocated in hypertonic saline group. Patients were studied for 7+/-6 days in the HS group and for 7+/-5 days in the mannitol group [p=NS]. Neurologic conditions at admission were not different between the two groups [Table 2]. Mortality and neurologic outcome did not differ between the two groups [Table 2]. In the mannitol group, 6 of 11 patients had an IVC vs. 9 of 14 patients in the HS group. The number of osmotic solute infusions was 3.8+/- 5.1 in the mannitol group and 3.4+/-4.5 in the HS group [p=NS]. The osmotic load was 174.2+/-18.1 mOsm per injection in the mannitol group and 331.5+/-35.4 mOsm in the HSS group. The number and duration of ICH episodes and decreases in CPP, the number of times IVCs were opened, and the daily cerebrospinal fluid flow for each group are reported in Table 3. Compared with the patients given HS, the 11 patients who were given mannitol had

Table 2: Neurologic severity among different groups

Parameter	Mannitol group [n=11]	Hypertonic Saline group [n=14]	p value
GCS on admission	5.36+/-1.4	4.9+/-1.4	0.23
ISS	32.2+/-7.8	36.5+/-8.5	0.5
SAPS II	41.9+/-12.5	46.3+/-11.4	0.36
Patients with Polytrauma	7 [63.6%]	11 [78.6%]	NS
Findings of CT scan			
I] Shift 0-5mm, cisterns present	0	0	NS
II] Cisterns compressed/absent	3	5	NS
III]Shift>5 mm	6	7	NS
IV] Surgically evacuated lesion, any	2	2	NS
Follow up at day 60			
I] Dead	4 [36.4%]	5 [35.7%]	NS
II] GCS severe	7 [63.6%]	8 [57.1%]	NS

Table 3: Effects of 2ml/kg body weight 20% Mannitol [174.21+/-18.1 mOsm per injection] or 2ml/kg body weight 7.5% Hypertonic Saline [331.54+/-35.4 mOsm per injection] on episodes of increased ICP, the need to open IVC or treatment failure

Parameter	Mannitol Group [n=11]	HS Group [n=14]	p
ICP>25 mm Hg			
I] Episodes/day	14.6+/-3.4	7.1+/-2.9	0.009
II] Total duration of episodes [min/day]	93.4+/-37.2	62.6+/-28.1	0.03
CPP<70 mm Hg			
I] Episodes/day	4+/-2.2	3.2+/-1.7	0.29
II] Total duration of episodes [min/day]	56.5+/-24.2	61.2+/-25.2	0.91
Intraventricular Catheter [IVC]			
I] No of times opened/day	20.7+/-8.4	7.7+/-4.7	0.000 36
II] Cerebral fluid drained/day	98.1+/-22.9	56.3+/-21	0.000 26
Treatment failure	6/11	1/14	0.01

more episodes of elevated ICP [p=0.009], and the daily total time of ICP >25 mm Hg was significantly longer [p=0.03]. Episodes of CPP <70 mm Hg were not different in the two groups. In patients with IVC, the daily rate of catheter opening and the daily cerebrospinal fluid drained were significantly higher in the mannitol group than in the HS group [p=0.003 and p=0.002, respectively].

Treatment failure was significantly higher in the mannitol group [6 of 11 patients] than in the HS group [1 of 14 patients, p=0.01].

During the period in which patients received osmotherapy, comparisons of electrolyte and hydrotic changes are expressed in table 4. Water balance was significantly higher in HS group compared to those in mannitol group [p=0.008], although sodium balance was similar in both the groups [p=0.06]. Plasma osmolality was significantly higher in HS group [p=0.03] but its variation was similar to that of mannitol group [p=0.06]. Although variation of natremia was higher in HS group but it did not reach up to the level of statistical significance [p=0.23]. Hemodynamic management, fluid loading and vasopressor infusions were similar in both the groups [Table 4].

Table 4: Changes of haemodynamics and fluid-electrolyte balance

Parameter	Mannitol group [n=11]	HS group [n=14]	p value
Water balance [ml/day]	283.7+/-179	609.6+/-243.3	0.008
Sodium balance [meq/day]	61.4+/-20.1	45.6+/-19.4	0.06
Osmolality [mOsm/kg] within 4 hours of osmotherapy	298.4+/-13.4	312.7+/-16.5	0.03
Variation in osmolality [mOsm/kg] from before infusion value	4.3+/-3.2	11.8+/-5.8	0.06
Hypernatremia within 4 hours [mmol/l]	148.2+/-5.9	147.6+/-6.4	0.83
Variation of Na^+ from before infusion level [mmol/l]	2.3+/-1.1	5+/-1.6	0.23
Hydroxyethyl starch administered during study period [ml]	1109.1+/-335.3	834.5+/-380.6	0.07
Dopamine infusion during study period [µg/kg/min]	10.5+/-2.7	8.1+/-3.2	0.05
Norepinephrine infusion during study period [µg/kg/min]	0.35+/-0.18	0.44+/-0.2	0.25

DISCUSSION

In the present study the superior efficacy of 2ml/kg body weight 7.5% hypertonic saline [331.5+/-35.4 mOsm] over 2ml/kg body weight of 20% mannitol [174.2+/-18.1 mOsm] was clearly suggested by the fact that the number of episodes of ICH were about two times lower and duration of such episodes were about 1.5 times lower in HS group compared to mannitol group. It was also observed from the results of the study that the failure rate of HS was significantly lower than that of mannitol. The number of times of opening of IVC and amount of drained cerebrospinal fluid were also significantly lower in HS group. All these findings suggest that HS was more effective than mannitol.

The efficacy of hypertonic saline in reducing ICP was known for a long time although the mechanism of action remains controversial. There are different hypothesis regarding the mechanism of reduction of ICP by HS. The first hypothesis is administration of HS causes a reduction of volume of cerebral cells, therefore a reduction of ICP[6,12,21,22]. The second hypothesis links the vascular expansion induced by the infusion, which, leads to an increase in mean arterial pressure. If the autoregulation of cerebral blood flow persists, the increase in mean arterial pressure will lead to vasoconstriction in cerebral arteries, causing a reduction in cerebral blood volume, which explains the reduction in ICP[22]. According to the third hypothesis the reduction of vascular volume is related to improvement in blood rheology provided cerebral autoregulation remains intact[23,24]. Fourth, the osmotic effect can cause a reduction in the volume of cerebrospinal fluid[24].

The first published work of mannitol for the treatment of ICH was way back in 1961[25]. Mannitol is an inert substance, not metabolised in the body, freely filtered in the kidney and not reabsorbed[26]. The distribution volume is roughly equal to the extracellular compartment[27]. The pharmacologic data for mannitol depend on experimental model chosen, the number of injections administered and the choice of duration of the study. In short, the effects of a single injection are rapid, the maximum efficacy at the end of injection ranging from 30-60 mins and return to baseline values in 2 to 10 hours[20]. The increase in osmolality in clinical studies ranged from 15-25 mOsm/kg[28,29]. The chief problem is rebound effect by diffusion of mannitol in the injured tissue. In one study, mannitol alone normalized ICP in 25% of patients[30]. Experimental and clinical results shown that an injection of mannitol has reduced ICH by about 5 mm Hg[20,30,31,32]. In human beings the gain in CPP is due to fall in ICP, with mean arterial pressure remaining constant[32]. The effects of mannitol are delayed until a gradient of osmolality is being established between plasma and cells[19], although it would appear that mannitol acts before intracellular is being diminished[33]. According to some authors mannitol should not be used when plasma

osmolality exceeds 320 mOsm/l[30].

First used in the beginning of the 1900s, HS again returned to the forefront of the interest in 1980s for the management of hypovolemic shock[34,35]. Experimentally and clinically HS infusion acts in a manner which is analogous to mannitol[16,18,36]. Some studies have shown that in patients with moderately increased ICP 2ml/kg HS reduced ICP and increased CPP significantly[37]. Maximum effect was reached at around 60 minutes after HS administration. Experimentally sudden hypernatremia reduces intracerebral water, which persists for 24-48 hours and disappears after 1 week[38,39]. The observed reduction of ICP were found to be close to that obtained from mannitol [5 mm Hg][19] or sometimes even higher [15-20 mm Hg][20,40], hemodynamic stability was improved hence CPP was maintained. Potential risks with the HS are hyperosmolality, hypernatremia, convulsions, coma, cerebopontile myelinosis, hypokalemia, congestive cardiac failure, increase in intracerebral bleeding or subdural haematomas, haemolysis and coagulation problems[3,22,34]. Usually symptoms occur at osmolality >350 mOsm/kg and experimentally it correlates with the speed of increase in hypernatremia. The danger level of Na^+ at which the symptoms appear is empirical 150-155 meq, as per some studies[41], however sudden increase in natremia more than 30 mmol/l will certainly lead to lesions[42]. HS was found to be as effective as mannitol in neurosurgery in reducing brain bulk and ICP[36]. There is documentation that mannitol decreases the production of CSF[32], but we have not found any study which directly addresses the effects of hypertonic saline on CSF formation. Indirectly, however, HS might reduce CSF formation via increase in serum osmolality. This has been documented with glycine[33].

In our prospective study, we have included those patients admitted to neuro-ICU for severe head trauma. The relatively less number of patients in both the groups were due to several factors. The recent guidelines do not recommend osmotherapy as primary management, hence reduces the need of such interventions[12]. Most of the episodes of ICH were related to tracheal suctioning, noxious stimulation, and insufficient level of sedation. As per our protocol these patients were initially managed with opening of IVC and draining of CSF, then blood pressure was increased as and when necessary, or the patient was subjected to hyperventilation. At the end only 25 patients, 11 of which were in the mannitol group, and 14 in the HS group could be included. Studied with larger sample sizes are required to verify whether the findings of this study. The present study was designed to evaluate the medium term efficacy of ICH treatment. This study was not intended to evaluate the influence of the kind of osmotherapy on mortality and recovery. Osmotherapy is only one kind of treatments used for severe head trauma patients, and a considerable number of patients will be required to study the variable. This is the reason why we have selected the number of ICH episodes as the main variable along with, as secondary variables, the duration of ICH episodes, the number and duration of reductions in CPP, the daily amount of CSF drainage and the rate of clinical failure of osmotherapy. The criteria for efficacy of a given hyperosmotic solute have not been standardized. In our study, we maintained a pragmatic attitude toward the criteria for treatment failure: we considered that the maximum effect of the infusion was reached in 10 mins after the end of the infusion. Because it is accepted that an infusion of mannitol can be repeated after the failure of the first dose, it seemed logical to wait for two successively ineffective infusions for the same ICH episode before concluding a therapeutic failure. Mannitol is the standard solute for hyperosmolar therapy, thus it was necessary to compare the new treatment with mannitol[12]. Because we wanted to study the effect of a more hyperosmolar solute without other modification of fluid administration and modality of infusion, we chose to use hypertonic saline at 7.5%, which provides twice as many osmoles as mannitol for the same volume infused. Also, it is a common choice to use these two solutes at the same dose of infusion of 2 mL/kg when hyperosmolar therapy is instituted[17,36,39].

CONCLUSION

In conclusion, the present study suggests that increasing the osmotic load during osmotic therapy (from 174.2+/-18.1 of 20% mannitol to 331.5+/-35.4 mOsm of HS) was followed by a better efficacy on the number and the duration of established ICH episodes in head injured patients requiring osmotic therapy. Also, the failure rate of 2 ml/kg body weight administration of HS was significantly lower than that of 2 ml/kg body weight administration of 20% mannitol. This increased osmotic load with hypertonic saline was not achieved at the expense of hypernatremia and serum osmolality, which remained within acceptable levels. Within the limitation of the present study, these data suggest that 2 ml/kg HS

(approximately 480 mOsm per 70 kg body weight) is an effective and safe treatment for ICH episodes in head-injured patients when osmotherapy is indicated.

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