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Mannitol Vs Hypertonic Saline in the Treatment of Increased Intracranial Pressure in Traumatic Brain Injury Patients

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Abstract
Medical management of increased intracranial pressure should include sedation, drainage of cerebrospinal fluid, and osmotherapy with either mannitol or hypertonic saline. The aim of this study is to compare the effects of equimolar doses of 20% mannitol solution and of 7.45% hypertonic saline solution (HS) in elevated intracranial pressure of traumatic brain injury patients. This study was conducted at Mamatha medical college, it includes 20 patients divided into 2 groups; mannitol group (M), and Hypertonic saline(HS)group. A single equimolar infusion (255 mOsm dose) of either 231 ml of 20% mannitol (M)or 100 ml of 7.45% hypertonic saline (HS) administered for 20min. Intracranial pressure, arterial blood pressure, cerebral perfusion pressure,brain tissue oxygen tension, serum sodium and osmolality, and urine output were measured at T0,30,60,90,120 min. The two drugs were efficient in reducing ICP. At 60 mins after the start of theinfusion, ICP was reduced by 44% ±17% of baseline values (mean ± SD) in the mannitol group vs. 33% ±12% of baseline values in the HS group. The CPP was elevated significantly in mannitol group compared to base line values whereas slight elevation was seen in HS group. Significantly greater increase inurine output notice in mannitol than HS, although there was no difference in the vascular filling requirement between the two treatments. HS caused a significant elevation of serum sodium and chlorideat 120 mins after the start of the infusion. It was concluded that equimolar dose of both drugs were effective in treatment of elevated intracranial pressure.

Keywords-*Mannitol, hypertonic saline, intracranial pressure, traumatic brain injury.*

INTRODUCTION

Increased intracranial pressure (ICP) to >20 mm Hg is associated with increased morbidity and mortality after brain injury [1]-[3]. Intracranial hypertension may lead to a reduction in cerebral blood flow [4], which can lead to further morbidity. Cerebral oedema results from a variety of mechanisms thought to include vasoregulatory dysfunction, extravasation after microvasculature damage, and the accumulation of intra-cellular and interstitial osmotically active substances [5].

Osmotherapy has been the cornerstone of the medical management of cerebral oedema, irrespective of its aetiology, for decades, and mannitol is the most widely used agent [6]. Mannitol is widely used in the management of raised

intracranial pressure (ICP), for renal protection in cardiac, vascular, and renal transplantation surgery, and in the management of rhabdomyolysis. It has also previously been used for bowel preparation before colorectal surgery.

Mannitol exerts its ICP-lowering effects via two mechanisms—an immediate effect because of plasma expansion and a slightly delayed effect related to its osmotic action. The early plasma expansion reduces blood viscosity and this in turn improves regional cerebral micro vascular flow and oxygenation. It also increases intravascular volume and therefore cardiac output. Together, these effects result in an increase in regional cerebral blood flow and compensatory cerebral vasoconstriction in brain regions where auto regulation is intact, resulting in a reduction in ICP. Cardiac output may subsequently decrease to lower than baseline levels because of the peripheral vasodilatation induced by mannitol and care must be taken to ensure that cerebral perfusion pressure is maintained at this time. Mannitol also establishes an osmotic gradient between plasma and brain cells, drawing water from the cerebral extracellular space into the vasculature, thereby reducing cerebral oedema. An intact blood–brain barrier (BBB) is a prerequisite for mannitol osmotic action and cerebral oedema may be worsened by mannitol administration if the BBB is disrupted [7].

The application of alternative osmotic agents to mannitol, such as hypertonic saline (HS), has been explored. The effects of HS were first described by Weed and Mckibban in 1919, but it is only recently that evidence for their potential benefit in the management of intracranial hypertension has emerged. In addition to an osmotic action, HS has haemodynamic, vasoregulatory, immunological, and neurochemical effects [8]. In particular, HS relaxes arteriolar vascular smooth muscle and, in association with a reduction in cerebral endothelial cell oedema, improves cerebral microcirculatory flow. It also expands intravascular volume, thereby potentially augmenting cerebral perfusion pressure. Through these multiple actions, HS reduces cerebral oedema and ICP and improves cerebral blood flow and perfusion pressure.

There is some evidence that HS is effective at reducing raised ICP resistant to mannitol and that it has a more favourable effect than mannitol on mortality after TBI [9]. However, there are no large, randomized comparisons of HS against mannitol, or long-term functional outcome studies, proving its superiority[8]. Continuous infusion and bolus administration of HS have been investigated as alternatives to mannitol to reduce brain swelling and ICP, particularly in the context of TBI [7],[8]. However, HS is available in concentrations varying from 1.7% to 29.2% and different protocols for its administration have been described and tested in clinical studies. Three per cent saline is usually used for continuous infusion and 23.4% for bolus administration. There is no definitive evidence defining the optimal osmolar load or duration or timing of treatment for raised ICP [8]. It is important to monitor plasma sodium concentration during administration of HS, aiming for a value between 145 and 155 mmol litre^{-1}. HS must be administered via a central venous catheter because of its potential to cause thrombophlebitis. Side-effects include rebound increases in ICP, volume overload, coagulopathy, and electrolyte abnormalities, particularly hypernatremia and hyperchloraemic metabolic acidosis.

The aim of this study is to compare equimolar mannitol and hypertonic saline in the treatment of increased intracranial pressure with regards to brain and systemic parameters.

MATERIALS AND METHODS

This prospective study was performed in the intensive care unit at the Mamata General Hospital, Khammam after obtaining approval from the hospital ethics committee. All the patients recruited to the study had brain injury and required an ICP monitor as part of their management. Informed consent was obtained from the patients' relatives, and all the patients were >18 years old were included in this study, if the ICP increased to >20 mm Hg for >5 mins, and this was not related to a transient external noxious stimulus or systemic derangement.

Twenty patients were had sustained a traumatic brain injury. All patients were intubated, mechanically ventilated, assessed clinically, and had ICP monitoring. Monitored cardiovascular variables included electrocardiogram, invasive blood pressure, MAP, central venous pressure, and cardiac output when indicated. Adequate hydration and nutritional support were provided. Midazolam was used as sedative, appropriate analgesia with fentanyl and atracurium as muscle relaxant were administered if required. Vasoactive or inotropic support (noradrenaline and dobutamine) were administrated to maintain CPP at>70 mm Hg and MAP at >90 mm Hg. A single equimolar infusion (255 mOsm dose) of 231 mL of 20% mannitol (Mannitol group) and 100 mL of 7.45% hypertonic saline (HS group) during 20 mins of administration.

For all patients static cerebral auto regulation test was performed because the response to osmotherapy may differ according to the pressure auto regulation status. Before intervention, a blood sample was obtained to determine the baseline serum sodium concentration, haemoglobin and osmolality and repeated every 30 mins after the start of infusion (T30, T60, T90) until the end of the study period (T120). Blood levels of sodium, chloride, glucose, and creatinine were collected at T0 and at T120. No therapeutic intervention (e.g., nursing procedure, manipulation of ventilatory variables, changes in vasoactive support and in sedative drug regimens) was allowed during the experiment, If patients required any therapeutic intervention or developed respiratory, hemodynamic, or neurologic instability during the study period, they were excluded from the analysis.

Statistical Analysis: Data (Mean ± SD) are expressed as percentage of baseline values obtained at the reference time T0 (%). To examine differences between groups of patients in their response to osmotherapy, interaction between groups and serial measurements was tested using two-way analysis of variance for repeated. Comparisons between the two groups were subjected to a Student's *t*-test (intergroup analysis). Frequency data were compared using the chi-square test. Statistical significance was declared when $p < 0.05$.

RESULTS

The 20 enrolled patients had traumatic brain injury was continued the treatment. The demographic data was shown in table 1.There was no significant difference between the two groups with regard to age, sex and weight. All the base line parameters were given in the table 2 and they were comparable with each other.

Table 1.Demographic Data

parameter	M group	HS group
Age (years)	32.52±10.23	35.26±8.62
Sex M/F	8/2	7/3
Weight (Kgs)	53.24±7.24	56.32±9.45

Both the study drugs mannitol and HS reduced the intracranial pressures efficiently at all-time intervals of 30, 60, 90 and 120 minutes when compared to base line parameters of T0. The ICP changes were comparable between the two groups of patients over study time period.

Table 2.comparison of baseline(T0) physiological parameters in two groups

parameter	Mannitol	Hypertonic saline
ICP mm of Hg	30±4	27±4
CPP mm of Hg	76±10	79±12
MABP mm of Hg	106±13	107±11
Heart Rate beats/min	77±8	78±6
CVP mm of Hg	6±6	7±6
Temperature c	36±1.4	36±1.2
PaO2 mm Of Hg	192±20	198±22
PaCO2 mm of Hg	34±7	32±6
Arterial pH	7.40±.05	7.42±0.03
Serum osmolality mOsm/kg	294±10	297±13
Serum sodium mmol/L	142±6	141±8
Serum chloride mmol/L	108±5	106±7
Hemoglobin g/L	112±10	114±13
Serum glucose mmol/L	7.2±4.0	7.3±3.5
Serum creatinine µmol/L	50±14	54±11

Values were expressed in mean ±SD.

The CPP was elevated significantly in mannitol group compared to base line values whereas slight elevation was seen in HS group. The mean arterial blood pressure was remained unchanged throughout the study period in two groups. There was transient increase in heart rate at T30 and T60 in mannitol

group although no significant interaction was found between treatments and temporal course of heart rate. There was a transient decrease in haemoglobin in the mannitol group at T30.The Relative changes (Δ%, mean±SD) expressed as percentage of baseline values (T0) inphysiological data after the infusion of mannitol or hypertonic saline solution was shown in table 3.

Table.3 Relative changes (Δ%, mean±SD) expressed as percentage of baseline values (T0) innphysiological data after the infusion of mannitol or hypertonic saline solution

parameter	T30	T60	T90	T120
ICP % mm of Hg				
Group M	-40±10	-44±19	-34±10	-32±11
Group HS	-36±15	-35±12	-31±15	-25±10
CPP % (mm of Hg)				
Group M	+20±21	+23±21	+13±15	+16±14
Group HS	+7±11	+9±8	+8±10	+6±6
MABP % (mm of Hg)				
Group M	+2±8	+1±9	+1±10	+2±7
Group HS	-3±6	-1±9	-1±7	0±7
HEART RATE % (beats /min)				
Group M	+10±10	+8±12	+5±11	+3±9
Group HS	+6±9	+7±10	+7±7	+5±9
SERUM OSMOLALITY (mOsm/kg)				
Group M	+2±2	+2±1	+1±1	+1±1
Group HS	+2±1	+2±1	+2±1	+1±1
HEMOGLOBIN %				
Group M	-6±6	-4±6	-2±5	-1±3
Group HS	0	0	0	-1±2

The Central venous pressure, PaO_2, $PaCO_2$ and arterial P^H remain unchanged during the study. Urine output was significantly higher in the mannitol group than in the HS group. Four patients in the both group required a volume of hydroxyethyl starch ranging between 250 and 500ml. There was no difference in the vascular filling requirement between the two treatments. Temporary and minor increases in measured serum osmolality noticed at T30 and at T60, but there was no difference in between two groups. However, the magnitude of serum sodium and chloride changes (i.e., the T120-T0 difference) was higher after the hypertonic saline infusion.

DISCUSSION

The present study was conducted at the Mamata medical college, Khammam. 20 patients were included in the study and it is aimed to investigate immediate effects of an osmotic compound in a single dose infusion for 20min.

Mannitol was recommended as the first-line osmotic agent for the treatment of intracranial hypertension attributableto traumatic brain injury [10]. Numerous studies had shown that mannitol was effective in decreasing intracranial pressure [11]. Despite mannitol being the most commonly used osmotic diuretic in the emergency and intensive care management of intracranial hypertension, there was no evidence to guide the optimal dose and duration of treatment [12]. Management protocols therefore vary from unit to unit. The ICP effect of mannitol was dose-dependent and higher doses also provide a more durable reduction in ICP [12]. The current guidance recommends that 0.25–1.0 g kg^{-1}mannitol should be given by i.v. infusion over 20–30min [6]. The peak ICP effect of mannitol occurs within 30–45 min and lasts around 6 h. Mannitol becomes less effective with repeated doses and, in any case, multiple administrations can result in an unacceptably high serum sodium and osmolality that was associated with neurological complications, including osmotic demyelination syndromes. 'Rebound' increases in ICP can also occur after the initial reduction because of eventual passage of mannitol into the brain. This phenomenon can occur with any osmotic agent but appears to be particularly associated with mannitol administration. In 2007, the Cochrane collaboration reviewed the use of mannitol after acute TBI and concluded that although it is effective in reversing acute brain swelling, its role in the on-going management of severe TBI remains unclear [9].

However, mannitol had many clinically important adverse effects, such as renal failure and hypovolemia [13],[14]. These adverse effects of mannitol have led to increasing enthusiasm about the use of hypertonic saline formulations, which can reduce ICP without causing volume contraction and with less risk of nephrotoxicity[15]. Several

randomized clinical trials have suggested that sodium-based hypertonic solutions may be superior to mannitol in reducing ICP [16][17].

In the present study the magnitude of ICP reduction in the HSS group was in line with other studies using a comparable osmotic load (250–260 mOsm) of HSS [17],[18]. We found that the duration of ICP reductionafter the bolus of HSS was prolonged, with no evidence of return to baseline values at 120 mins, as previouslyreported [18], [19]. Despite these ICP changes after HSS treatment, CPP changes did not reach significance in this group of patients because the range of CPP changes was proportionally of less magnitude than that of ICP changes when MABP remained unchanged, explained by a reduction in brain volume through a direct osmotic action.

Our results with mannitol were in comparison the studies using a similar osmotic load (220–250 mOsm) of mannitol [20],[21]. The mannitol-induced ICP effect was prolonged, and no evidence of a rebound was found during the 120-min study period. Paczynski et al [22] indicates that the rate of infusion could be involved in the duration of the effect of mannitol: the faster the infusion, the more likely would be the termination of effect through a rapid renal elimination or a penetration of mannitol into brain tissue. These marked ICP findings resulted in a significant sustained CPP increase in the mannitol group and were associated with dramatic changes in cerebral hemodynamics an increase in FVm along with an improvement in cortical microcirculation, using laser-Doppler flowmetry [20]. According to the Poiseuille law, a change in microvascular blood viscosity induced by mannitol is a possible mechanism, as it may increase CBF, enhancing the effects on ICP. The transient decrease in blood haemoglobin in the mannitol group is indirectly in line with this assumption. This hypothesis agrees wellwith the admitted effects of mannitol onreducing blood viscosity [22]. No changes in PbrO2 were noted, despite steady improvements in CPP after mannitol infusion [21]. At present, we can formulate that the therapeutic action of mannitol is likely to combine osmoticaction and improvements in CPP and brain circulation, whereas oxygen delivery to the brain seems to be unaffected [23]. Urine output after mannitol infusion, acting as a diuretic, was higher than after HSS [23],[24]. The two osmotic compounds transiently increased serum osmolality, and HSS caused elevation of serum sodium, as previouslyreported [8],[17],[24].

CONCLUSION

A single equimolar infusion (255 mOsm dose) of 231 ml of 20% mannitol (Mannitol group) and 100 ml of 7.45% hypertonic saline (HS group) were efficient in decreasing intracranial pressure in traumatic brain injury patients. Pretreatment factors, such as serum sodium, systemic hemodynamics, and brain hemodynamics, should be considered while choosing these drugs.

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