Original research article

Comparative assessment of hypertonic saline versus mannitol in the treatment of raised intracranial tension in children

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Abstract

Aim: to assess the efficacy of hypertonic saline versus mannitol in the treatment of raised intracranial tension in children.

Material and methods: This comparative and observational study was done the Upgraded Department of Paediatrics, Patna Medical College and Hospital, Patna, Bihar, India, for six Months. Total 220 Children aged 2 to 18 years admitted to the emergency Department of Pediatrics during the study period with clinical symptoms and signs of raised intracranial pressure were included in this study. Group A: 110 patients treated with mannitol. Group B: 110 patients treated with 3% hypertonic saline. Loading dose (5ml/kg) was followed by maintenance dose (2 ml/kg) in every 6 h in both groups for two days (osmolarity of mannitol and 3% hypertonic saline are almost same i.e. 1100 mOsm/l and 1098 mOsm/l, respectively).

Results: Decrease in MAP was highly significant (P<0.001) at 0 h in males 0 h, 6 h in females, and moderately significant at 12 h, 36 h in females and significant(P<0.05) at 6, 24h, 42h 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 in osmolality and mortality (fisher Z). 3% hypertonic saline was more efficacious than mannitol in the initial 12 h and equally or more efficacious than mannitol therapy later. Decrease in coma hours was a significant additional finding in the group treated with 3% hypertonic saline. Group B. Change in blood biochemistry was within acceptable limits in Group B.

Conclusion: the mannitol has several side effects, 3% hypertonic saline is a safe and effective alternative inmanaging cerebral edema.

Keywords: Hypertonic saline, mannitol, raised intracranial pressure

Introduction

Hypertonic saline (HTS) or mannitol are being routinely used to treat intracranial hypertension.[1-5] Mannitol acts through its osmotic diuretic properties that produce a reduction in brain water content and cerebrospinal fluid (CSF) pressure in approximately 20 min.[6] Besides this, it also reduces intracranial pressure (ICP) through the changes in blood fluid dynamics or blood rheology. Recently, HTS has appeared an appealing alternative to mannitol because its reflection coefficient is higher than that of mannitol (1.0 vs 0.9, respectively). Thus, HTS does not cross the intact blood–brain barrier.[7] Due to this property, HTS causes a greater increase in serum osmolality as compared to mannitol in equiomolar dosage. HTS creates a greater transendothelial osmotic gradient that results in more water movement from interstitial and intracellular brain to the intravascular space. HTS little diuretic effect and thus maintains hemodynamic stability and cerebral perfusion pressures.[8] Previously published clinical trials comparing the effects of HTS and mannitol have included

the patients with varied intracranial pathologies. The protocols of administration of HTS or mannitol and the osmolar load of the compounds were also variable.[7,9-13] Wu et al. compared these two agents in elective supratentorial tumors for brain relaxation. They excluded the patents with signs of raised ICP. The authors found that brain relaxation was better in the HTS group than the mannitol group during elective supratentorial brain tumor surgery. Rozet et al.[7] also compared 20% mannitol and 3% HS for brain relaxation in patients scheduled to undergo craniotomy for varied neurosurgical pathologies and found that there was no difference in brain relaxation between two groups. The aim of the present study to determine the efficacy of hypertonic saline in the treatment of raised intracranial tension in children in comparison to mannitol.

Material and methods

This comparative and observational study was done the Upgraded Department of Paediatrics, Patna Medical College and Hospital, Patna, Bihar, India, for six Months , after taking the approval of the protocol review committee and institutional ethics committee.

Total 220 Children aged 2 to 18 years admitted to the emergency Department of Pediatrics during the study period with clinical symptoms and signs of raised intracranial pressure were included in this study. Patients with compromised renal function (increased Serum, creatinine, hepatic encephalopathy, serum Na+ (>150 meq/l), diabetic ketoacidosis and cerebral malaria were excluded from the study.

Groups

Group A: 110 patients treated with mannitol.

Group B: 110 patients treated with 3% hypertonic saline.

Methodology

Loading dose (5ml/kg) was followed by maintenance dose (2 ml/kg) in every 6 h in both groups for two days (osmolarity of mannitol and 3% hypertonic saline are almost same i.e. 1100 mOsm/l and 1098 mOsm/l, respectively). Blood pressure was measure at admission and then in every 6 h, both pre and post drug (30 min of 3% hypertonic saline or mannitol therapy. S. creatinine were measure before starting treatment and after 48 h. Blood urea nitrogen were measure before starting treatment and after 48 h. Serum electrolytes measure before starting treatment and then in every 12 h. ABG also measure before starting treatment, and after 12, 24, 36 and 48 h.

CT scan (or MRI when needed) of head: Comparison of average reduction of mean arterial pressure (pre and post drug) at definite time (6h) intervals was done to indirectly assess reduction in intracranial pressure.

Results

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 in osmolality and mortality (fisher Z). 3% hypertonic saline was more efficacious than mannitol in the initial 12 h and equally or more efficacious than mannitol therapy later. Decrease in coma hours was a significant additional finding in the group treated with 3% hypertonic saline. Group B. Change in blood biochemistry was within acceptable limits in Group B.(table 1-5)

Table 1: Age and Sex wise distribution of trial groups

Groups	Mean age	Female		Male	
	(mths)	No. of cases	%	No. of cases	%
A	66.7	40	36.36	70	63.64
B	67.3	42	38.18	68	61.82
	Total	82	37.27	138	62.73

Table 2: Etiological distribution of trial group

Etiology	Group A	Percentage	Group B	Percentage
Meningoencephalitis	77	70	81	73.64
Neurocysticercosis (Anoxic Encephalopathy)	14	12.73	9	8.18
Head trauma	8	7.27	9	8.18
Space occupying lesion	7	6.36	6	5.45
Global Infarction	4	3.64	5	4.54

Table 3: Comparison of various parameters between group A & B

Parameter (X±SD)	Group A	Group B	't' value	'*P*' value	Inference
S. Osm (mosm/kg)	311±4.5 (280-320)	307±5.2 (289-323)	1.39	>0.05	Not Significant
S.Na (meq/l)	127±2.1 (121-132)	137±6.7 (121-154)	6.22	<0.001	Highly Significant
Duration of coma (hrs)	99.1±21.32 (27-137)	76.49±13.12 (23-143)	8.39	<0.001	Highly Significant
S.Chloride (mmol/l)	96.6±1.3 (84-98)	102±1.8 96-107)	3.21	<0.05	Significant
Mortality	6	5	Z=0.29 Fisher Z	>0.05	Not Significant

Table 4: Relationship between group A and group Bmale subjects

Hrs	Group A (X±SD)	Group B (X±SD)	't' value	'*P*' value	Significance of B
0	7±3.27	11.5±4.51	6.31	<0.001	Highly Significant
6	7±2.51	8.3±3.61	2.17	<0.05	Significant
12	5.7±1.65	5.7±1.90	0.96	>0.05	Not Significant
18	6.6±2.92	6.2±2.7	1.11	>0.05	Not Significant
24	6.2±2.62	5.1±2.50	2.61	<0.05	Significant
30	4.7±2.11	4.1±2.57	1.63	>0.05	Not Significant
36	3.3±2.63	3.7±2.26	0.71	>0.05	Not Significant
42	2±2.21	2.7±2.41	2.07	<0.05	Significant
48	2±1.91	1.8±1.17	0.34	>0.05	Not Significant

Table 5: Relationship between group A and group Bfemale subjects

Hrs	Group A) (X±SD)	Group B (X±SD)	't' value	'*P*' value	Significance of B
0	7±1.91	8.3±1.70	4.85	<0.001	Highly Significant
6	5.8±1.22	4.5±2.31	3.17	<0.001	Highly Significant
12	5.0±1.41	6.2±1.82	2.97	<0.01	Moderate Significant
18	2.7±1.12	3.2±1.87	1.60	>0.05	Not Significant
24	3.4±1.97	4.1±2.23	1.33	>0.05	Not Significant
30	4.6±1.21	3.37±1.11	3.27	<0.01	Moderate Significant
36	4.2±1.36	4.39±1.31	0.59	>0.05	Not Significant
42	2.6±1.79	3.1±1.60	1.31	>0.05	Not Significant
48	1.6±1.74	1.32±0.61	1.33	>0.05	Not Significant

Discussion

For the first time, in 1919, Weed and McKibben14 reported in animal models that HS results in a change in the brain volume. However, HS failed to attract the interest and field of application it deserved. In the early 1980's, its positive effects were shown in patients with hemorrhagic shock.15 Later, it was employed in animal models with traumatic cerebral edema and shown to be superior than mannitol in reducing intracranial pressure (ICP) and fluid content of brain.16,17These experimental findings gave encouragement for application to patients with cerebral edema of traumatic origin. Worthley, et al.18 demonstrated reduction in ICP and increase in systemic perfusion with a 30% saline given as a single bolus in two traumatic mannitol resistant patients. Like-wise, in a few uncontrolled studies HS at 3-23.4% has been shown to reduce the ICP after head trauma.[19,20]

During the period in which mannitol was used intensively, maintenance of serum osmolarity below 320 mOsm/l was recommended because of complications of acute tubular necrosis (ATN) and renal failure. However, it was later understood that this complication developed as a result of dehydration and hypovolemia.21 Children have been found to tolerate well the rather high serum osmolarity (365 mOsm/l) due to HS.22,23 Owing to its diuretic effect and the consequent risk of development of hypovolemia, mannitol has a greater risk of being complicated by ATN than HS. Comparative studies with mannitol have also been conducted and published. In a prospective, randomized study, Vialet, et al.24 showed that HS at 7.5% concentration administered as an isovolemic bolus (2 ml/kg) was more effective than 20% mannitol in reducing the ICP in trauma patients. Another prospective study conducted by Horn, et al.25 using 7.5% saline administered as bolus infusion to patients with elevated ICP due to trauma and not responding to the standard treatment showed that it was effective in reducing the ICP and CPP. With the aim of reducing the ICP to below 20 mmHg, Peterson, et al.22 administered a 3% saline infusion to 68 children with trauma who did not respond to standard treatment. They found serum-Na concentrations of 150-170 mEq/l and a serum osmolarity of 300-330 mOsm/l to correlate with better prognosis. Our study is a prospective analysis of one year period with a patient population consisting of children. Our cases and etiologic factors are different from other studies. In our study, the etiologic factors included were infection, hemorrhage, anoxia, and trauma factors. ICP measurement could not be conducted in our study, so treatment was continued considering the serum-Na concentration and osmolarity until clinical improvement was achieved. We have shown better results in Group B with no significant side effects. However, compared with mannitol, the clinical efficacy has also been confirmed by mortality assessment.

Hypertonic saline has been used more frequently in trauma, intracerebral hemorrhage, burn and stroke patients. Our patient group was different in their etiology of brain edema. Rationale of use of mannitol and HS is similar in both traumatic and non traumatic cerebral

edema because all cerebral edemas with varied etiologies usually have vasogenic mechanism. In addition, HS is more effective and safer than mannitol. Greater efficacy of HS compared to mannitol can be speculated by different reflection coefficients of these agents.26 Because the reflection coefficient for Na and Cl was 1.0, such a side effect in saline treatment may not be expected. In terms of the efficacy and side effect profile of the saline treatment in brain edema, the optimum serum- Na concentration and osmolarity are not known. In a retrospective study Peterson et al.22 though making no comparative analysis, suggested that prognosis in patients with serum-Na concentration within the range of 150-170 mEq/l and serum osmolarity of 300-340 mOsm/l seems to be better. Also, some studies report an inverse relationship between serum-Na concentration and ICP. 20-22 There was no significant difference in our patients with Na level of 150-160 and 160-170 mEq/l in terms of duration of the comatose state and mortality. As during the hyperosmolar state, to maintain the osmotic balance, idiogenic hyperosmoles are formed within the cells in 72-96 h.27-30 So after the termination of HS, serum-Na concentration should be gradually reduced over a period of more than two days. Potential side effects of hypertonic saline have been reported. 31 Myelinolysis, acute tubular necrosis and renal failure, subdural hematoma or effusion, heart failure, pulmonary edema, hypokalemia, hyperchloremic metabolic acidosis, coagulopathy, intra-vascular hemolysis, and rebound cerebral edema may occur. Myelinolysis occur more frequently if there is a rapid transition from hyponatremia to hypernatremia. For myelinolysis to occur, a daily serum-Na concentration load of 35-40 mEq/l is required.32 The region most susceptible to myelinolysis is the pontine white matter with visualized MRI and central pontine myelinolysis is manifested clinically as lethargy and quadriplegia/paresia. We have not observed acute flaccid paralysis/plegia after saline treatment. Especially, in patients with significant degrees of cerebral injury, the clinical assessment of this complication could not be detected possibly by the fact that they had blunted mental status. Renal failure, congestive heart failure, pulmonary edema, hypokalemia and phlebitis were not observed in any of our patients. There was no significant tendency for hemolysis or hemorrhage associated with acute fall in the hematocrit level.

Conclusion

We concluded that the treatment of cerebral edema of infectious, anoxic, hemorrhagic and traumatic origin, administration of HS is probably more effective and safer than mannitol. However, to determine just when to initiate treatment, how long to continue treatment, and target serum- Na concentration requires monitoring of the intracranial pressure. Further studies are required to resolve these concerns.

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