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## Effectiveness of 3% saline versus mannitol in children with cerebral oedema of non traumatic etiology

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### Abstract:

**Objective:** A randomized controlled trial was undertaken at the pediatric intensive care department of a tertiary care Pediatric hospital at Chennai, to evaluate the effectiveness of 3% saline as an anti-edema measure in comparison to mannitol in children with non-traumatic coma.

**Subjects:** The study comprised of 40 children with cerebral edema in each group.

**Outcome measures:** The outcome was analyzed in terms of survival/death, duration of coma and complications.

**Results:** Study parameters like age, gender, Glasgow coma scale, etiology of coma, signs of cerebral edema and duration of coma were comparable among the two groups and did not reveal statistically significant difference. Among the complications shock ( $p=0.03$ ) and dehydration ( $p=0.045$ ) were more common in children who received mannitol and hypernatremia ( $p=0.026$ ) was common in children who received 3% saline. The mortality rates among the two groups did not reveal statistically significant difference ( $p=0.07$ ).

**Conclusions:** In the treatment of cerebral edema of non traumatic origin in children, 3% saline can be considered as effective and safe as mannitol.

**Keywords:** Mannitol, 3% saline, cerebral edema

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### Introduction

Effectiveness of 3% saline as an anti-edema agent in comparison to mannitol among children admitted with cerebral edema of non traumatic etiology in the pediatric intensive care unit of a tertiary care children hospital was studied. A randomized open labeled controlled trial, was conducted at the Department of Pediatric Intensive Care, Institute of Child Health and Hospital for children, Egmore,

Chennai. Study was done during the period November 2008 to October 2010. Children in the age group of 3 months to 12 years, with cerebral edema of any etiology other than trauma admitted in the pediatric intensive care unit (PICU) and satisfying the criteria of diagnosis, were included.

Criteria for diagnosis of cerebral edema[1] Low GCS ( $\leq 8$ ) with any one of the following, persistent posturing after correction of shock and hypoxemia, unequal, dilated or

non-reacting pupil, cranial nerve palsies (3 and 6), bradycardia, hypertension, abnormal respiratory pattern, papilledema and/or radiological finding in CT brain. CT features were effacement of the basal cisterns, thin, slit like or completely obliterated ventricles, obliterated cortical sulci, shift in midline and temporal lobe or cerebellar tonsillar herniation. Children with cerebral edema but presenting with shock, renal failure or intracranial bleed on admission at PICU were excluded, as the hospital protocol in these children is to avoid mannitol. Children presenting with afebrile status epilepticus, with or without previous history of seizures, who show clinical recovery in 6 – 8 hours were not included. Children treated with antiedema measures prior to PICU admission were excluded. Any of the features in criteria of diagnosis if explainable by other causes like exposure to toxin or venom (snake bite, drug poisoning) were excluded. Any child who needed change of anti edema measures in view of complications due to therapy was excluded during analysis.

#### Method

80 children who satisfied the inclusion criteria were recruited during the study period. The diagnosis of cerebral edema was made as per the diagnostic criteria given above. Two groups were chosen: A - mannitol and B - 3% saline. Children were assigned to group A (mannitol) and group B (3% saline) with the help of computer generated random numbers. The study was approved by institutional ethical committee. Informed written consent was obtained from parents or caregivers.

Children in group A, were treated with 20% mannitol. In group B, children were treated with 3% saline. The treatment otherwise was identical as per the protocol of the intensive care unit in both groups. 20% mannitol was given at a dose of 1.5ml/kg IV, over 20 minutes, every 8 hours. 3% saline was given in a dose of 5ml/kg IV, over 20 minutes, every 8 hours. Electrolytes and urea creatinine were monitored every 8 hours. Serum sodium was targeted to be maintained between 145-155 mEq/dl[2]. Maximum duration of treatment of cerebral edema was 72 hours. Electrolytes, urea and creatinine were monitored 8 hourly. Treatment for cerebral edema was not continued if child developed complications like shock and renal failure necessitating termination of therapy.

Symptoms, clinical signs, fundus examination, CT finding and lab investigations were compared between the study groups. The outcome was analyzed in terms of

survival/death, duration of coma and complications. Complications recorded were hypernatremia, coagulopathy, pulmonary edema, subarachnoid hemorrhage, hemolysis and renal failure. Probable cause of cerebral edema such as CNS infection, DKA, hepatic encephalopathy, infarct and tumors was arrived at using the clinical criteria and lab investigations. Etiologies were grouped into infective, metabolic and others. Both group A and B were sub analyzed in terms of outcome with respect to age and etiology.

**Statistical methods:** Data were analyzed with SPSS 14.0. All values are presented as mean and SD. Statistical significance was analyzed by Student t-test. The level of significance was set at  $P < 0.05$ .

#### Results

Out of the 40 children in each group 35 (87.4 %) children in the mannitol group and 32 (80%) children in the 3% saline group completed the study. 13 children could not complete the study as per protocol; 10 children died before improvement of cerebral edema and within 72 hrs in mannitol group and in 3% saline group and 3 children were switched from mannitol to 3% saline due to fluid refractory shock which developed during mannitol therapy. The mean age group of the children was  $59.17 \pm 42$  and  $46.47 \pm 36.68$  months in groups A and B respectively ( $p = 0.11$ ). Gender distribution was comparable in both the groups with a male preponderance. 60 % of the mannitol group and 62% of the saline group were due to infective causes ( $p = 0.75$ ) other causes included hepatic encephalopathy, diabetic keto acidosis, inborn errors of metabolism, space occupying lesion and infarcts. Study groups have been compared in Table -1.

The Glasgow coma scale was comparable among the mannitol group and 3% saline group  $6.77 \pm 1.352$  (3-8) vs.  $6.04 \pm 1.51$  (4-8) ( $p = 0.06$ ). Clinical signs like unequal pupils, absent doll's eye movement, 3<sup>rd</sup> and 6<sup>th</sup> nerve palsy, posturing, hypertension, bradycardia and focal neurological deficit were comparable between the two groups. The duration of coma among those who completed the study ranged between 13-146 hrs in mannitol group and 28-260 hrs in saline group. The mean and  $\pm 2$  standard deviation were  $59.8 \pm 29.7$  and  $78.9 \pm 50.8$  hours respectively ( $p = 0.06$ ). The duration of coma due to different aetiology and across different age groups did not reveal any statistically significant difference. Complications encountered have been shown in the Table- 2.

**Table 1. The comparison between two study groups**

Study parameter	Mannitol group n=40	3% saline group n=40	P-value
Male:female	22:18(1.2:1)	26:14(1.8:1)	0.49
Mean age (months)	59.17 ±42	46.97 ± 36.68	0.114
Etiology infective metabolic others	25(62.5%) 12(30%) 3(7.5%).	24(60%) 11(27.5%) 5(12.5%)	0.75
GCS scale range	3-8	4-8	0.057
Duration of coma(hrs)	13-146	28-260	0.063
Mortality	15(37.5%)	24(60%)	0.07

**Table 2. Complications among the study groups**

Study group	Hypernatremia	Coagulopathy	Dehydration	Pulmonary edema	Hemolysis	Renal Failure	Shock	SAH
Mannitol	0	4	11	2	0	2	11	0
3%saline	6	9	4	1	1	4	3	1
P value	0.026*	0.225	0.045*	1	1	0.67	0.03*	1

Serum sodium at the time of recruitment into the study was comparable between the groups: 128 – 135mEq/dl in mannitol group and 129 – 134 mEq/dl in 3%saline group. Maximum and minimum serum sodium values attained during the study (132-137meq/dl in mannitol and 145-157meq/dl in 3%saline group) were significantly higher in 3%saline group (p – 0.00). 6 cases in 3% saline group had serum sodium levels > 155mEq/dl during the therapy, hence subsequent doses was skipped until the serum sodium levels decreased to 155mEq/dl. 37.5% in the mannitol group and 60 % of the 3% saline group died overall.

Mortality rates did not reveal any statistically significant difference among the two groups (P- 0.07).

#### Discussion

The most rapid and effective means of decreasing cerebral edema is osmotherapy. Osmotic therapy is intended to draw water out of the brain by an osmotic gradient. Mannitol is the most popular osmotic agent. Mannitol, an alcohol derivative of simple sugar mannose, was introduced in 1960 and has since remained the major osmotic agent of choice in the management of cerebral edema. Mannitol has been shown to have no adverse electrolyte imbalances when used

in cerebral edema [3]. In the early 1980's, positive effects of isotonic saline were shown in patients with hemorrhagic shock [4]. Subsequently studies showed the usefulness of hypertonic saline as an osmotherapy in cerebral edema [5, 6]. Hypertonic saline solutions have evolved as an alternative to mannitol and they are used in otherwise refractory intracranial hypertension. In intensive care settings, hypertonic saline has been found to have reduced intracranial hypertension after subarachnoid hemorrhage, brain trauma, and a variety of other brain diseases, including cerebral edema in acute liver failure [7]. Hypertonic saline solutions have gained renewed interest and, recently more common application in neurocritically ill patients have been described. [8, 9, 10].

Hypertonic saline (HS) is as effective as mannitol for treatment of raised intracranial pressure in traumatic brain injury in children. Plasma sodium of up to 160-170 mmol/L have been targeted to control ICP. HS may produce less rebound intracranial hypertension compared to mannitol which cannot be easily removed from intracellular space. HS does not cause obligatory osmotic diuresis and hence is likely to preserve or augment plasma volume rather than deplete it. Mannitol may precipitate acute renal failure and may not be excreted in oligo-anuria whereas HS is renoprotective. HS directly increases plasma Na, any measurable changes in blood osmolality can be easily monitored by measuring plasma Na. The effect of mannitol on plasma osmolality can only be estimated using an osmole gap.

Like mannitol, hypertonic saline also possesses unique extra osmotic properties, including modulation of CSF production and resorption and accentuation of tissue oxygen delivery. Few studies have made direct comparisons between mannitol and hypertonic saline. In a prospective, randomized comparison of 2.5 ml/kg of either 20% mannitol (1400 mOsm/kg) or 7.5% hypertonic saline (2560 mOsm/kg) in patients undergoing elective supratentorial procedures, ICP and intraoperative clinical assessment of brain swelling were similar in both treatment groups [11].

Most of these study perspectives were from adult population and only few studies were available in pediatric population [12,13]. Both were studies on non traumatic etiology in pediatric populations. Our study is a prospective analysis done in children between ages of 3 – 140 months. This was comparable with the study done by Yildizdas et al., [12] (1-120mon) whereas the study by Upadhyay, et al [13] included adolescent population. In our study etiological factors included infective, metabolic,

infarct and space occupying lesion. This was comparable with other two studies.

In this study, male children were predominant similar to Upadhyay et al. In the study by Yildizdas et al, female population was predominant. Clinical signs and symptoms in our study were comparable with other studies. Glasgow coma scale in both the groups was  $6.77 \pm 1.352$  (3-8) and  $6.04 \pm 1.51$  (4-8). This was higher compared to Yildizdas et al. This was probably because in the present study, we recruited cases without shock. Cases with low GCS tend to have shock and were not recruited in our study.

The duration of coma in our study was  $59.89 \pm 29.67$  hours (mannitol) and  $78.91 \pm 50.84$  hours (3% saline). This was of shorter duration when compared to study by Yildizdas et al ( $123 \pm 48.2$ ;  $88.6 \pm 42.5$ ;  $87.5 \pm 26.1$ ). In our study, even though duration was higher in 3% saline group, this did not attain statistical significance. Overall mortality, age wise mortality and etiology wise mortality comparisons were not statistically significant in both the groups, similar to the study by Upadhyay et al. whereas the study by Yildizdas et al showed statistically decreased mortality in hypertonic saline group.

In terms of the efficacy and side effect profile of the 3% saline treatment in cerebral edema, the optimum serum-Na concentration and osmolality are still debatable. It was postulated to maintain the serum sodium between 145 – 155 mEq/dl (serum osmolality approximately 300-320 mOsm/L). In the present study, serum sodium was between 132-137 mEq/dl in mannitol and 145-157 mEq/dl in 3% saline group which was similar to the study by Upadhyay et al. (123-130; 122-153 mEq/dl).

Complications like dehydration and shock were significantly more in mannitol group and hypernatremia was significantly higher in 3% saline group. These complications were similar to other studies [12,13]. Besides, hypernatremia is an intended effect of intervention with hypertonic saline administration. Though coagulopathy and renal failure were more in 3% saline group there was no statistical significance ( $p = .225$  and  $0.67$  respectively). There was no significant tendency for haemolysis or haemorrhage observed in study. The limitation in our study is the fact that ICP monitoring was not done. This might have given some valuable information. However clinical efficacy has been compared between two groups by mortality assessment and duration of coma.

**Conclusion:**

To conclude, in the treatment of cerebral edema of non traumatic origin in children, 3% saline can be considered as effective and safe as mannitol. 3% saline may be preferred in situations like shock where mannitol cannot be used. However frequent monitoring of sodium is essential when 3% saline is used as an anti-edema measure.

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