3% SALINE VERSUS MANNITOL IN TREATMENT OF CEREBRAL EDEMA IN CHILDREN

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CERTIFICATE

This is to certify that the dissertation titled **"3% SALINE VERSUS MANNITOL IN TREATMENT OF CEREBRAL EDEMA IN CHILDREN"** submitted by Dr.D.KUMARAGURU to the Faculty of pediatrics, The Tamilnadu Dr. M.G.R. Medical university, Chennai in partial fulfillment of the requirement for the award of M.D. Degree (Pediatrics) is a bonafide research work carried out by him under our direct supervision and guidance, during the academic year 2008-2011

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This is submitted to **The Tamilnadu Dr. M.G.R. Medical University**, Chennai in partial fulfillment of the rules and regulations for the M.D. Degree Examination in Pediatrics.

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CONTENTS

INTRODUCTION

Intracranial hypertension is a common feature of many illness treated in PICU. The early signs and symptoms of intracranial hypertension tend to be nonspecific. The classic Cushings triad of bradycardia, hypertension, and apnea occurs late and often not manifest fully in children.

Most of our understandings and approach to treatment is based on studies of patients with traumatic brain injuries. Whether those concepts are directly relevant to the pathophysiologic processes involved in more global CNS injuries such as hypoxia, infection and metabolic disorders, remain a matter of debate.

Within constraints of a closed skull, an enlargement of brain tissue (cerebral edema), an increased volume of CSF, or an increased volume of blood or the presence of a space-occupying lesion (SOL) such as a tumour or an abscess will initially reduce the size of the other compartments and later increase intracranial pressure, once the compensatory mechanisms fail.

Cerebral edema

The brain occupies about 80% of the volume of the skull. Apart from solid tumours, increase in brain compartment is generally a result of cerebral edema. Cerebral edema is the most common cause for intracranial hypertension in children treated in PICU.

Types of cerebral edema

Cerebral edema can be divided into three forms: vasogenic, hydrostatic, and cytotoxic.

Vasogenic edema occurs in areas of inflamed tissue characterized by increased capillary permeability, and is most typical around CNS tumours, abscesses, and infarcts.

Hydrostatic or interstitial edema is a result of elevated CSF hydrostatic pressures. It occurs primarily in lesions associated with obstruction to CSF flow, and in a typical periventricular distribution.

Cytotoxic edema is the most common of the three forms seen in the PICU and is, unfortunately, the least easily treated. It occurs as a result of direct injury to brain cells, often leading to irreversible cell swelling and death. This form of cerebral edema is typical of traumatic brain injuries, infections, hypoxic ischemic injuries and metabolic disease.

Aetiology

Cerebral edema is seen in the following neurological and non-neurological conditions:

Neurological conditions -

a) Ischemic stroke and intracerebral haemorrhage

b) Brain tumours

c) Meningitis and encephalitis of all etiologies

d) Other brain infections like cysticercosis, tuberculosis and toxoplasma.

Non-neurological conditions -

a) Diabetic ketoacidosis, lactic acidotic coma

b) Malignant hypertension, hypertensive encephalopathy

c) Fulminant viral hepatitis, hepatic encephalopathy, Reye's syndrome

d) Systemic poisoning (carbon monoxide and lead)

e) Hyponatremia, SIADH

f) Opioid drug abuse and dependence

g) Bites of certain reptiles and marine animals

h) High altitude cerebral edema

Clinical Features

A high index of suspicion is very important. The features of cerebral edema add on to and often complicate the clinical features of the primary underlying condition. Until the ICP reaches a level that produces local ischemia, cerebral edema per se will not produce clinical neurological abnormalities.

Signs and symptoms [1]

Early – Poor feeding, vomiting, irritability, lethargy, seizures, hypertension

Late – GCS < 8, Coma, absent doll's eye movement, decerebrate responses, cranial nerve palsies, abnormal respirations, bradycardia, hypertension, and apnoea

Investigations

Urgent imaging is indicated in afebrile coma and in the presence of focal signs or papilledema, as the diagnosis includes stroke, intra-cranial bleed, tumour or hydrocephalus. However, any child who does not have a very obvious metabolic/ toxic cause for the coma generally requires to be imaged.

CT scan provides an excellent tool for in vivo determination of abnormalities in brain water content. The areas of edema appear as low density on unenhanced scan. This is due to the dilution of all the constituents of the white matter [*2*]. The anatomical specificity of CT permits detection of not only the presence but also the type of brain edema. This is helpful in differentiating nature of underlying lesion eg. infarction/tumour. However CT scan may be normal initially and it does not rule out raised ICP.

CT is also an excellent method for following the resolution of brain edema following therapeutic intervention.

An MRI may be more specific for early changes of herpes simplex encephalitis (where CT may be normal), posterior fossa and white matter pathology [*1*, *3*].

Invasive ICP monitoring is an important tool to monitor cases where cerebral edema is present or anticipated. Unfortunately, the direct measurement of ICP and aggressive measures to counteract high pressures have not yielded uniformly beneficial results, and after two decades of popularity - the routine use of ICP monitoring remains controversial. The problem may be partly a matter of the timing of monitoring and the proper selection of patients for aggressive treatment of raised ICP. Whether ICP monitoring adds much to the management of these patients is still open to question. Clinical signs and imaging data on shift of brain tissue are probably more useful

Treatment

Treatment of brain edema has not kept up with the advances in understanding of the mechanism producing the edema.

General measures

When signs of elevated ICP are present certain measures for management should be initiated.

Position of the patient - Elevation of head end of bed by 15-30 degrees to promote cerebral venous drainage is advisable and head is kept in midline to limit neck vein compression [*4*].

Correction of contributory factors - Correction of factors increasing ICP e.g. hypercarbia, hypoxia, hyperthermia, acidosis, hypotension and hypervolemia is helpful. Endotracheal intubation and mechanical ventilation to maintain PaCO2 in low 30s (controversial) [*1, 3*] may be helpful in impending herniation.

Hypothermia - Multiple mechanisms for reduced brain temperature-induced neuroprotection have been identified and include reduced metabolic rate and energy depletion, decreased excitatory transmitter release, reduced alterations in ion flux, reduced vascular permeability, edema and BBB disruption [*5*].

Fluid restriction - Fluid restriction minimally affects cerebral edema and, if pursued to excess, may result in episodes of hypotension, which may decrease cerebral perfusion pressure (mean arterial pressure – ICP) and is associated with worse neurologic outcome [*6*]. Fluid restriction is not warranted as a routine unless in specific situation like SIADH. Glucose containing solutions should be avoided; euvolemia should be maintained, 0.9%N or N/2 saline should be used; urinary losses should be replaced with 0.9%N saline in patients receiving mannitol; eventually to maintain mean arterial pressure [*4*].

Medical treatment

Osmotherapy

The most rapid and effective means of decreasing tissue water and brain bulk is osmotherapy [*2*]. Osmotic therapy is intended to draw water out of the brain by an osmotic gradient and to decrease blood viscosity. These changes would decrease ICP and increase cerebral blood flow (CBF).

Mannitol is the most popular osmotic agent. Mannitol has two distinct effects. The immediate effect is related to its rheological properties (decreased blood viscosity) resulting in a transient increased CBF followed by a more sustained fall in CBF [*1*]. The delayed osmotic effects occur after 15-30 minutes and last for 4-6 hours. IV Mannitol is given in the dosage of 0.25-0.5g/kg repeated 4-6 hourly. Mannitol should be avoided in case of hypotension, renal failure, serum osmolarity>320 mOsm/kg.

Hypertonic saline [HTS] is emerging as newer osmotherapy. Hypertonic saline can possibly affect the volume of the intracranial structures through various mechanisms. All or several of them are likely to be interacting to achieve the end result of hypertonic saline therapy:

reduction of cerebral edema and elevated ICP. These mechanisms [*7*] are summarised below:

- HTS also acts like mannitol by establishing a constant osmolar gradient in order to draw fluid from the brain parenchyma but without the risks of dehydration and tubular damage as in the case of mannitol. Hence it may be of more benefit in conditions where mannitol should be avoided.

- Reduced viscosity: Hypertonic saline enhances intravascular volume and reduces viscosity. The auto regulatory mechanisms of the brain vasculature have been shown to respond not only to changes in blood pressure but also to changes in viscosity. Thus, a decrease in blood viscosity results in vasoconstriction in order to maintain a stable cerebral blood flow.

- Increased plasma tonicity: It has been postulated, based on experimental animal data that increased plasma tonicity, such as that seen after hypertonic saline administration, favours more rapid adsorption of CSF.

- Increased regional brain perfusion, possibly secondary to dehydration of cerebral endothelial cells and erythrocytes, facilitating flow through capillaries.

- Increased cardiac output and mean arterial pressure, with resultant augmentation of cerebral perfusion pressure, most likely due to improvement of plasma volume and a positive inotropic effect.

- Diminished inflammatory response to brain injury, which has been demonstrated with hypertonic saline administration.

- Restoration of normal membrane potentials through normalization of intracellular sodium and chloride concentrations.

A variety of formulations of hypertonic saline solutions (2, 3, 7.5, 10, and 23%) [*8, 9*] are used in clinical practice for the treatment of cerebral edema either as bolus or continuous infusions. The goal in using hypertonic saline is to increase serum sodium concentration to a range of 145 to 155 mEq/L (serum osmolality approximately 300–320 mOsm/L) [*10*]

Corticosteroids

Corticosteroids lower intracranial pressure primarily in vasogenic edema because of their beneficial effect on the blood vessel. They have been less effective in cytotoxic edema [*11*].

Other agents

Barbiturates, procaine derivatives, indomethacin, propofol and THAM (Trihydroxy aminomethane) are some other agents which have been tried. Barbiturate coma is used in some centres in order to reduce the cerebral metabolic rate and thus the cerebral blood flow, although most references pertain to adults.

Surgical treatment

Surgical treatment is occasionally recommended for large hemispherical infarcts with edema and life threatening brain-shifts. Temporary venticulostomy or craniotomy may prevent deterioration and may be lifesaving [*12*].

Conclusion

Though there has been good progress in understanding of pathophysiological mechanisms associated with cerebral edema, more

effective treatment is required and is still awaited. Certainly, the “ideal” agent for the treatment of cerebral edema - one that would selectively mobilize and / or prevent the formation of edema fluid with a rapid onset and prolonged duration of action, and with minimal side effects, remains to be discovered.

REVIEW OF LITERATURE

I] Yildizdas D, Altunbasak S conducted a retrospective study to evaluate the efficacy and side effects of hypertonic saline[HTS] and mannitol use in cerebral edema in the Pediatric Intensive Care Unit Çukurova University, School of Medicine between June 2002 and May 2004 [*13*]. Patients treated with mannitol, HTS, or both mannitol and HS were assigned as Group I, Group II, Group III respectively. Cerebral edema and increased intracranial pressure were identified based on the clinical and/or radiological (CT, MR) findings. Clinical findings included low consciousness level (GCS <8) plus one or more of the followings: Unequal, dilated or unreactive pupils, loss of brain stem reflexes (light and oculocephalic), cranial nerve palsies (III, VI) and Cushing's triad. In Group I, patients were treated with 0.5 g/kg mannitol for the first two doses and if needed the maintenance doses were 0.25 g/kg/dose. In Group II, Hypertonic saline was given to provide a serum-Na level of 155-165 mEq/L. Extra boluses were given depending on the serum Na level. Group III received both mannitol and hypertonic saline. In Group I – 22, Group II – 25, Group III – 20 were recruited. There was no statistically significant difference between groups in terms of age (P = 0.5), gender (P = 0.4), Glasgow coma scale and etiological causes (P = 0.8). Mannitol was given for a total dose of 9.3 ± 5.0 (2-16) doses in

Group I, and 6.5 ± 2.8 (2-10) doses in Group III. Hypertonic saline was infused for 4-25 times in Group II. Although there was no statistically significant difference in the highest serum Na and osmolarity levels of the groups, duration of comatose state and mortality rate were significantly lower in Group II and Group III. Age, gender, cause of cerebral edema, electrolyte imbalance, hyperglycemia and hyperventilation had no significant impact on outcome. Limitations of this study: This was a retrospective study; Outcome variable of "duration of comatose state" included all patients irrespective of their survival status. Failure to sensor this time-to-event 'duration of coma' variable by mortality in this study could have been rectified. The p –value 0.003 while comparing the outcome of mortality (proportion) appears to have error. Using the factual data about mortality and survival given by authors in this study, the calculated P value is 0.07.

II] Piyush Upadhyay and Tripathi conducted a prospective randomized study to compare the efficacy and side effects of 3% saline and mannitol in management of raised intracranial pressure in children at GSVM Medical College, Kanpur [*14*]. 200 Children aged 2 to 18 months with clinical symptoms and signs of raised intracranial pressure were recruited. Patients with compromised renal function (increased serum creatine), hepatic encephalopathy, serum Na + (>150meq/l), diabetic ketoacidosis, cereberal malaria were excluded. Loading dose (5ml/kg) was followed by maintenance dose (2ml/kg) of mannitol or 3% hypertonic saline in corresponding groups for two days was administered. 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. Decrease in MAP was found to be highly significant ($p<0.001$) at 0 hr in males 0, 6 hr in females and moderately significant at 12, 36 hr in females and significant ($p<0.05$) at 6, 24, 42 hr in males in 3% saline group. Decrease in coma hours was a highly significant finding ($p<0.001$) in 3% saline group. No difference was noted in osmolality and mortality between both groups. Limitations of the study: Clinical criteria for raised intracranial pressure could have been clearly defined; mental status of the treated children could have been defined and considered for termination of treatment; side effects encountered during treatment could have been enumerated.

JUSTIFICATION

Cerebral edema is an important and frequent problem in neurocritically ill patient. This can result from various insults to the brain. Improving cerebral edema and decreasing ICP have been associated with improved outcome. However, all current treatment modalities are far from perfect and are associated with serious adverse events. Indiscriminate hyperventilation can lead to brain ischemia. Mannitol can cause intravascular volume depletion, renal insufficiency, and rebound ICP elevation; barbiturates are associated with cardiovascular and respiratory depression and prolonged coma; and cerebrospinal fluid drainage via intraventricular catheter insertion is highly invasive and may result in intracranial bleeding and infection. Other treatment modalities have been explored and hypertonic saline solution appears to be an appealing addition to the current therapeutic avenues for management of cerebral edema .Mannitol has been used extensively in treatment of cerebral edema in the past and is the time tested drug.

In clinical situations there are instances where mannitol is contraindicated such as when the child is in shock or renal failure. Mannitol is well known to produce rebound effect, serum electrolyte disturbances and hypovolemia and this has led to continued search of

newer agents. Hence there is a need for the use of alternate drugs like 3% saline in managing cerebral edema. 3% saline has been regularly used in patients with intracranial injury, stroke, and DKA and has been found to be useful. However the role of 3% saline in other causes of cerebral edema has not been studied in pediatric population. A Retrosepective study done in Turkey [*13*] has revealed that 3% saline seems to be more effective than mannitol in cerebral edema. In our PICU, 3%saline is used as a treatment for raised ICP since 2004. This study was done to analyze the effects of hypertonic saline in children with cerebral edema and to compare this treatment modality with mannitol in terms of efficacy, side effects and outcome.

AIM

To study the effectiveness of 3% saline as an antiedema measure in children admitted with cerebral edema in the pediatric intensive care unit of a tertiary care children hospital in a developing country.

SUBJECTS AND METHODS

STUDY DESIGN : Randomized Controlled Trial

PLACE OF STUDY : Pediatric Intensive Care Unit
Institute of Child Health and Hospital for Children, Egmore, Chennai.

PERIOD OF STUDY : November 2008 to October 2010.

STUDY POPULATION :

Children who are suspected to have cereberal edema between 3 months to 12 years.

INCLUSION CRITERIA:

Children in the age group of 3 months to 12 years, with cerebral edema of any etiology who satisfy the criteria of diagnosis, admitted in the PICU were included.

EXCLUSION CRITERIA:

(i) 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.

(ii) Child presenting with afebrile status epilepticus, with or without previous history of seizures, who show clinical recovery in 6 – 8 hours will not be included.

(iii) Children treated prior to PICU admission will be excluded.

(iv) Any of the features in criteria of diagnosis if explainable by other causes like neuroparalytic disorder (snake bite, GBS, drug poisoning) will be excluded.

CRITERIA OF DIAGNOSIS OF CEREBRAL EDEMA [*15*]:

Low GCS (<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
- Radiological finding like 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.

MANEUVER

80 children who satisfied the inclusion criteria were recruited during the study period. Two groups A and B were chosen. 40 children were assigned in each group with computer generated random number. The diagnosis of cerebral edema was made as per diagnostic criteria mentioned above. The study was approved by institutional ethical committee. Informed written consent was obtained from parents or caregivers.

In group A, children were treated with 20% mannitol. In group B, children were treated with 3% saline. The treatment otherwise were identical as per the PICU protocol in both groups. 20%mannitol was given at a dose of 1.5ml/kg IV, over 20 minutes, every 8 hourly [*16, 17*]. 3%saline was given in a dose of 5ml/kg IV, over 20 minutes, every 8 hourly [*16, 17*]. Serum sodium was targeted to maintain between 145-155 meq/dl. Treatment for cerebral edema was terminated at a GCS score > 8 and absence of other signs of cerebral edema as mentioned in inclusion criteria. Maximum duration of treatment of cerebral edema was 72 hours. Treatment was not continued if child developed complications necessitating termination of therapy.

The outcome was analyzed in terms of survival/death, duration of coma and complication. Other parameters included were symptoms, clinical signs, fundus examination, duration of ventilation, CT finding and lab investigations. Complications recorded were hypernatremia, coagulopathy, pulmonary edema, subarachnoid hemorrhage, hemolysis, renal failure. Probable cause of cerebral edema such as CNS infection, DKA, hepatic encephalopathy, infarct and tumors was arrived 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 etiological causes.

STATISTICAL ANALYSIS

Data were analyzed with SPSS 14.0. Chi square and t test were used for independent samples; ANOVA test was used for continuous variables. Brock chart was used where ever necessary.

PROFILE OF CEREBRAL EDEMA

Total cases recruited	80	100%
Total cases recruited in Mannitol group	40	50%
Total cases recruited in 3%Saline group	40	50%
Total cases completed the study in Mannitol group	35	43.7%
Total cases completed the study in 3%Saline group	32	40%
Cases not completed the study	13	16.3%

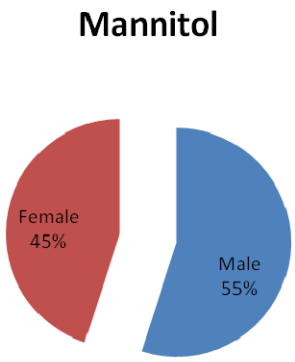
Cases not completed the study include the children who died before improvement of cerebral edema and within 72 hrs (n-10); and those who were switched from mannitol to 3% saline due to fluid refractory shock (n-3) which developed during mannitol therapy.

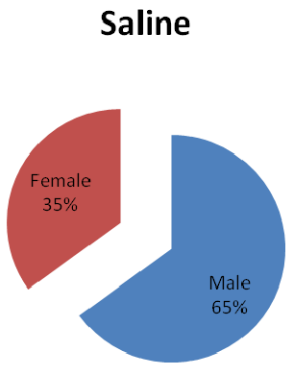
AGE OF PRESENTATION

	Mannitol	3%Saline	p - value
Mean (months)	59.17	46.47	0.114
SD	± 42.00	± 36.68	
Range	4 - 140	3 - 140	

- Age was comparable between both groups.

GENDER DISTRIBUTION

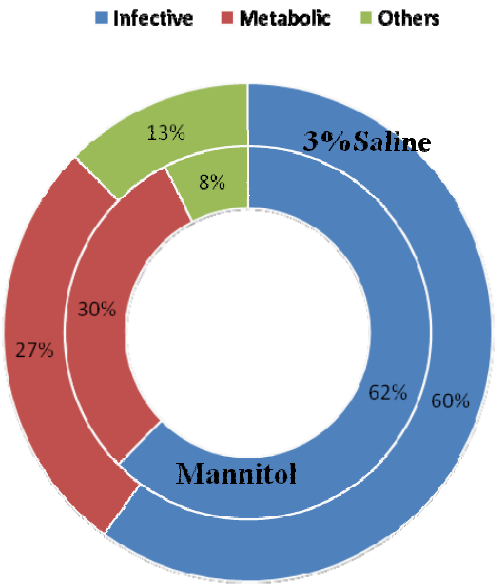




	Mannitol	3% Saline	p - value
Male	22	26	0.49
Female	18	14	
Total	40	40	

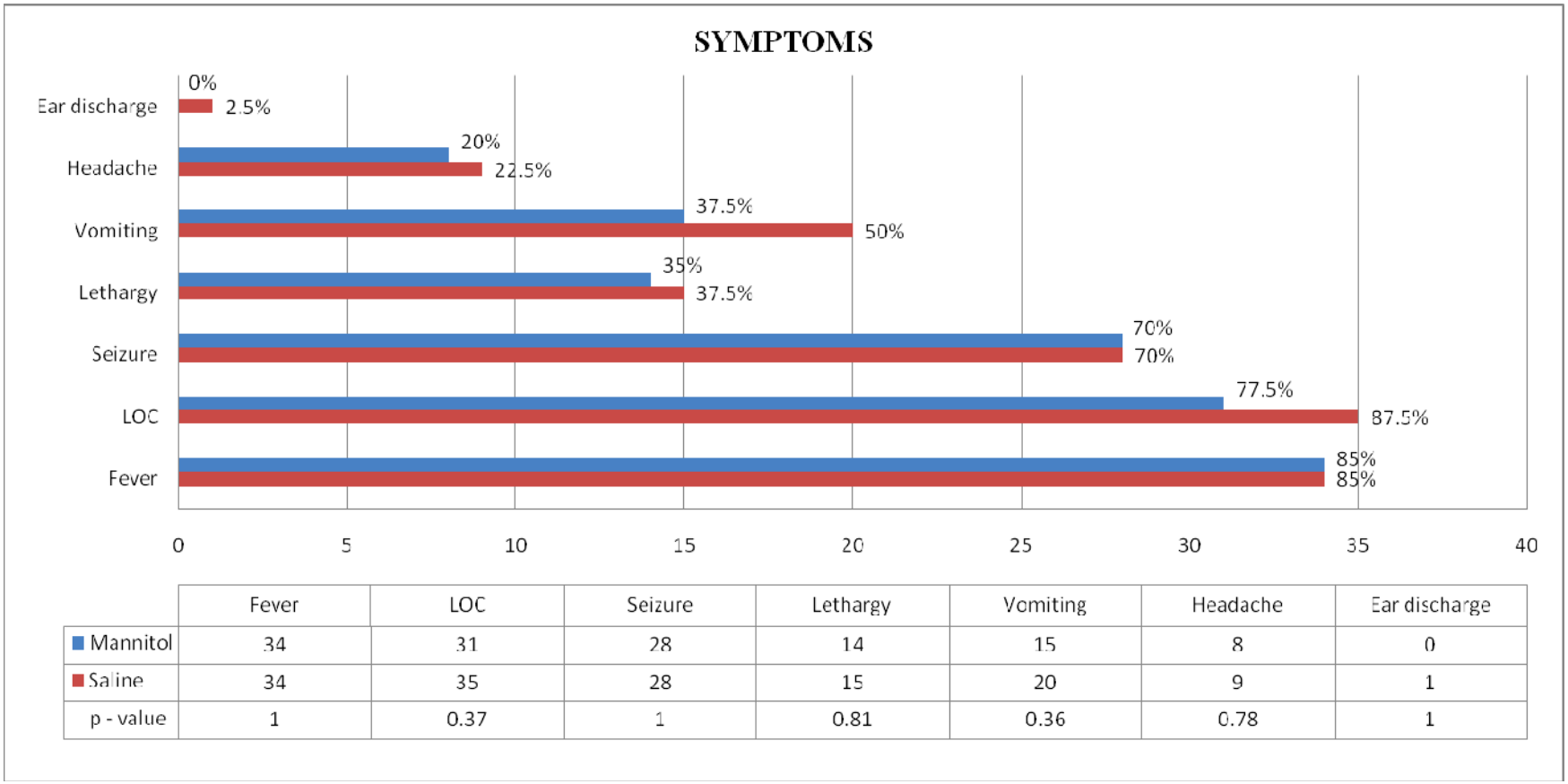
- Gender distribution was comparable in both groups. (p – value – 0.49)

ETIOLOGICAL DISTRIBUTION



Cause	Mannitol	3%Saline	p - value
Infective	25	24	0.75
Metabolic	12	11	
Others	3	5	
Total	40	40	

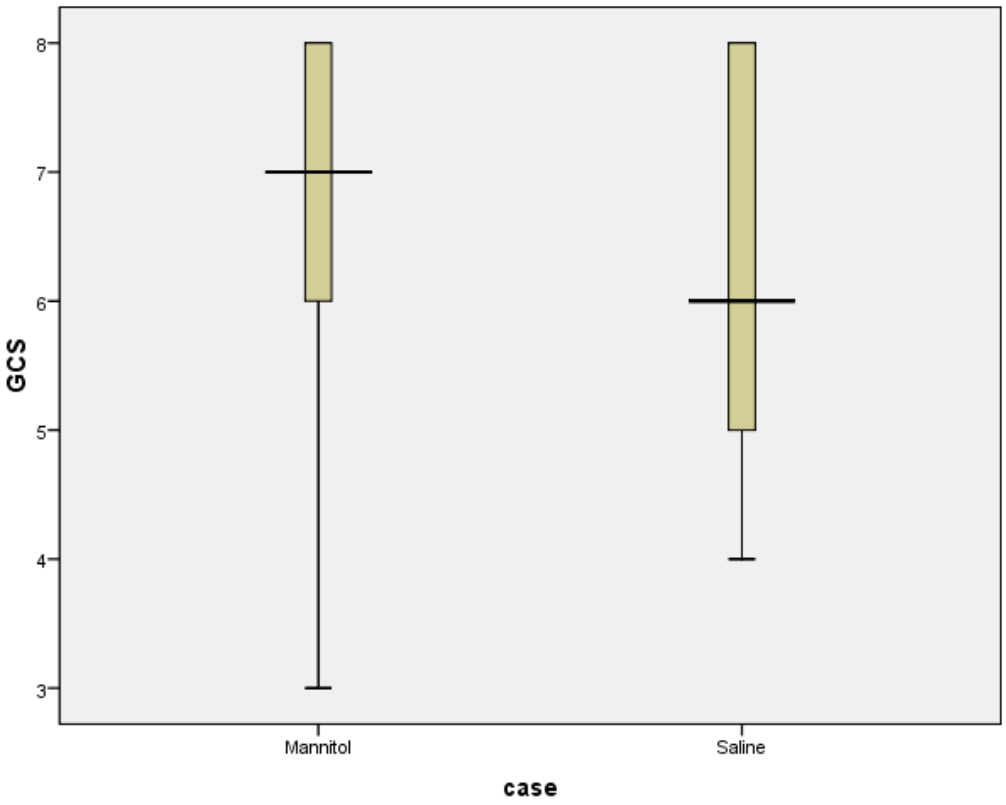
- Predominant cause for cerebral edema in both groups was infection. 62% in mannitol group and 60% in 3%saline group.
- Metabolic causes include diabetic ketoacidosis, hepatic encephalopathy and suspected inborn error of metabolism. Other causes include SOL, infarct etc



	Fever	LOC	Seizure	Lethargy	Vomiting	Headache	Ear discharge
Mannitol	34	31	28	14	15	8	0
Saline	34	35	28	15	20	9	1
p - value	1	0.37	1	0.81	0.36	0.78	1

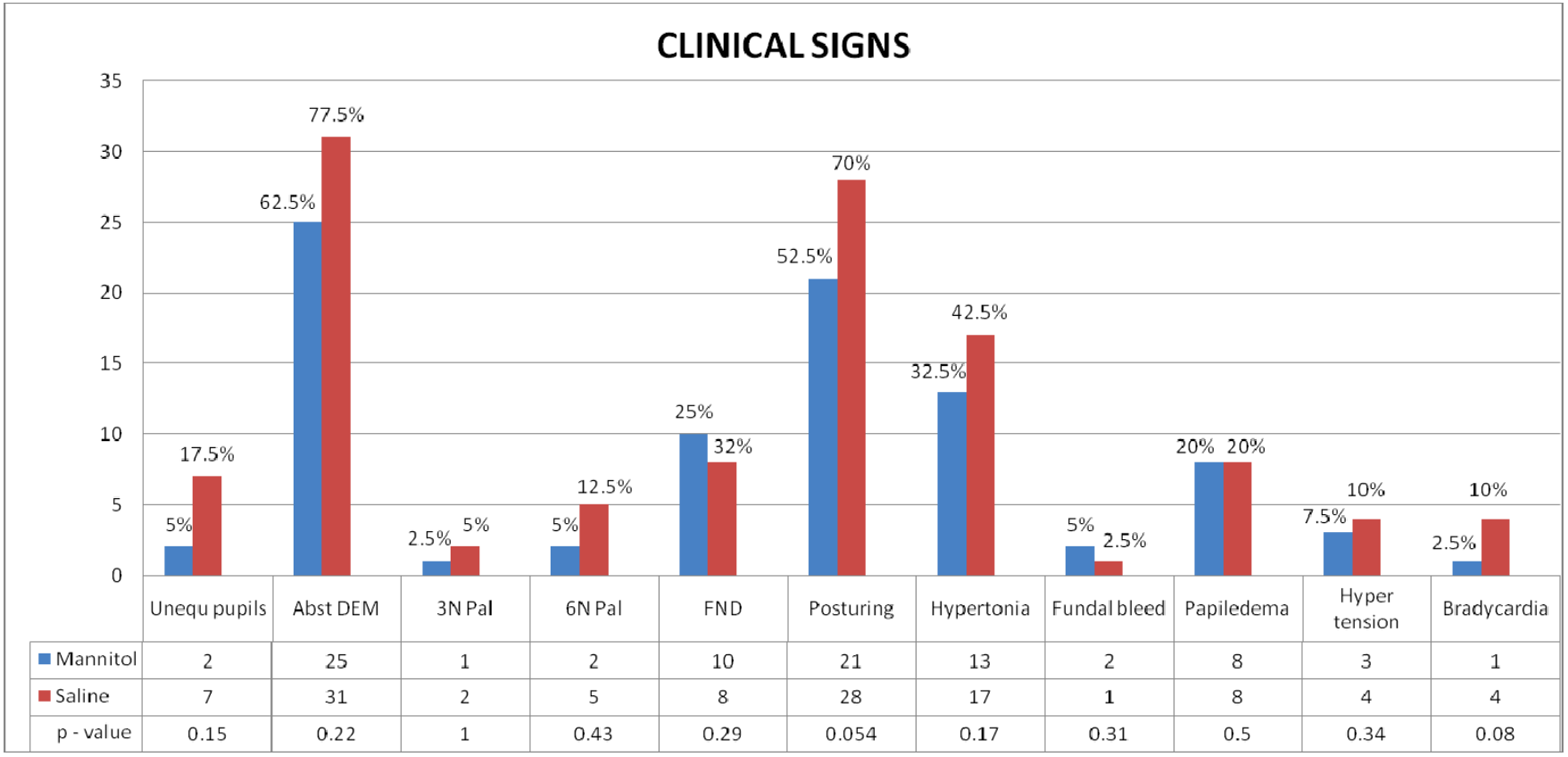
- Symptoms were comparable between both groups.

GLASGOW COMA SCALE



- Glasgow coma scale ranged between 3-8 in mannitol group and 4-8 in 3%saline group. GCS was comparable in both groups. (p – value – 0.057).

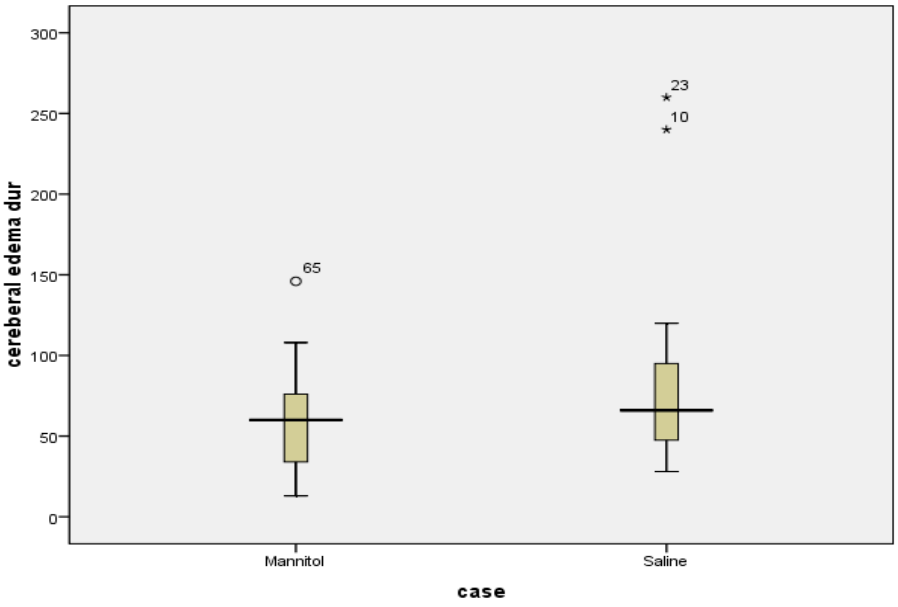
- In intubated children, GCS grimace score were used.



	Unequ pupils	Abst DEM	3N Pal	6N Pal	FND	Posturing	Hypertonia	Fundal bleed	Papiledema	Hyper tension	Bradycardia
Mannitol	2	25	1	2	10	21	13	2	8	3	1
Saline	7	31	2	5	8	28	17	1	8	4	4
p - value	0.15	0.22	1	0.43	0.29	0.054	0.17	0.31	0.5	0.34	0.08

- Clinical signs were comparable between both groups. [Abst DEM – Absent dolls eye movement; 3N Pal – 3rd nerve palsy; 6N Pal – 6th nerve palsy]

DURATION OF COMA



	No. of cases completed therapy	Mean (hrs)	Standard deviation	Range (hrs)
Mannitol	35	59.89	29.67	13 - 146
3%Saline	32	78.91	50.84	28 - 260
		P – value 0.063		

- Duration of coma was compared only for those who completed the therapy.
- Duration of coma was ranged between 13-146 hrs in mannitol group and 28-260 hrs in Saline group.
- Even though the duration of coma seems to be more in 3%saline group, there was no statistical significance.

AGE COMPARISION OF DURATION OF COMA

Age (mon)	Group	N	Mean (hrs)	Std. Deviation	p - value
<12	Mannitol	4	67.25	41.70	0.35
	3%Saline	7	50.71	15.41	
13-60	Mannitol	16	63.12	33.60	0.18
	3%Saline	16	84.43	52.66	
>60	Mannitol	15	65.06	37.49	0.20
	3%Saline	9	91.00	60.97	

- Duration of coma in different age groups was not statistically significant between mannitol and 3%saline.

ETIOLOGICAL COMPARISION OF DURATION OF COMA

Cause	Group	N	Mean (hrs)	Std. Deviation	p - value
Infective	Mannitol	23	67.30	67.25	0.35
	3%Saline	20	87.20	50.71	
Metabolic	Mannitol	9	56.77	63.12	0.18
	Saline	8	64.87	84.43	
Others	Mannitol	3	65.33	65.06	0.20
	3%Saline	4	65.50	91.00	

- Duration of coma in different etiological groups was not statistically significant between mannitol and 3%saline.

OVERALL MORTALITY

Outcome	Mannitol		3%Saline		Total	
	No	%	No	%	No	%
Survived	25	62.5%	16	40.0%	41	51.2%
Died	15	37.5%	24	60.0%	39	48.8%
					p-value – 0.07	

- 62.5% survived in mannitol group. 40% survived in 3%saline group.
- Mortality between the groups was not statistically significant. (p - 0.07)

AGE COMPARISION OF MORTALITY

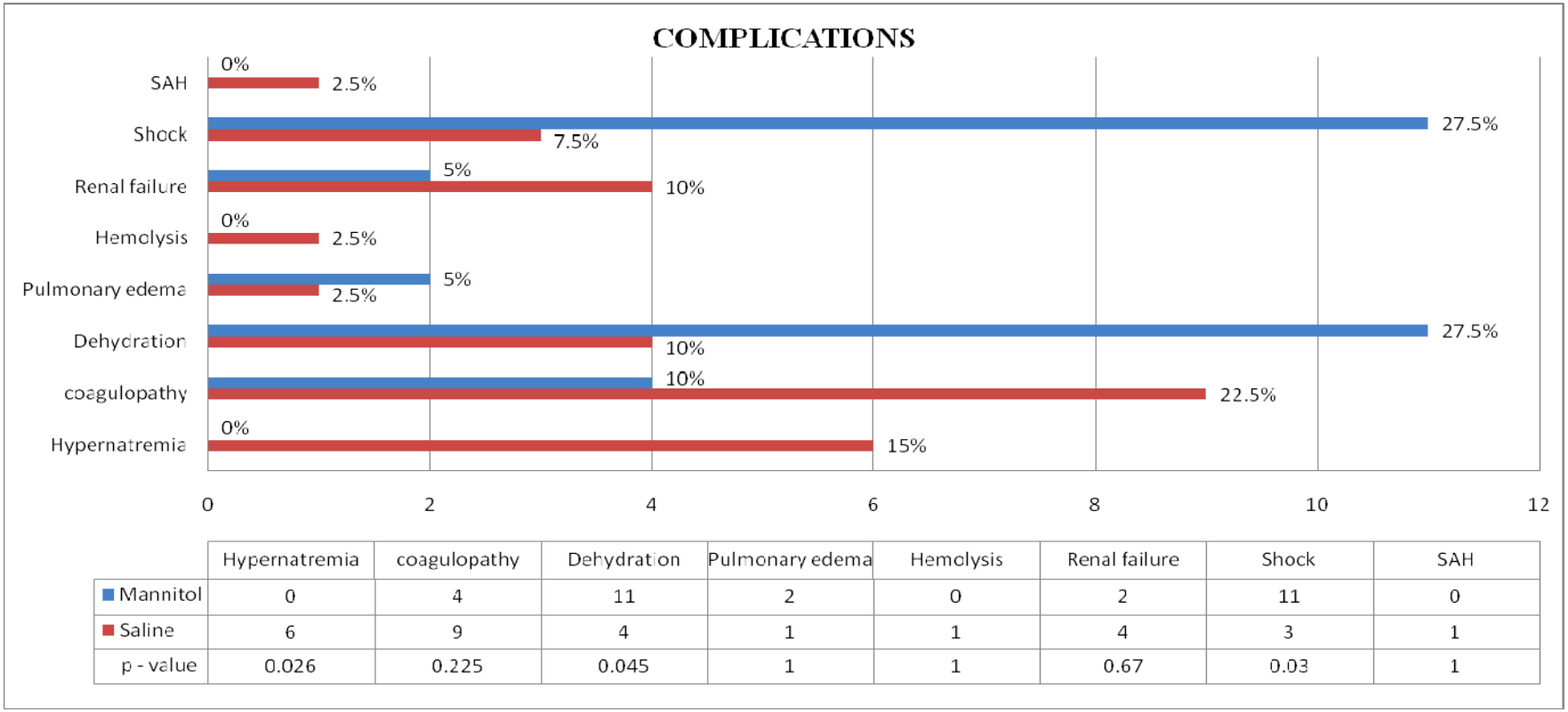
Age (months)	Mannitol	3%saline	p - value
≤ 12	4 (10%)	4 (10%)	0.29
13 - 60	7(17.5%)	14 (35%)	0.058
≥ 60	4(10%)	6 (15%)	0.06

- Age wise comparisons of mortality were not statistically significant between the two groups.

ETIOLOGICAL COMPARISION OF MORTALITY

Cause		Mannitol		3%saline		p - value
		Count	%	Count	%	
Infective	Survived	15	60.0%	10	41.7%	.258
	Died	10	40.0%	14	58.3%	
Metabolic	Survived	8	66.7%	3	27.3%	.100
	Died	4	33.3%	8	72.7%	
Others	Survived	2	66.7%	3	60.0%	1.000
	Died	1	33.3%	2	40.0%	

- In different etiological groups, mortality was not statistically significant between the two groups.

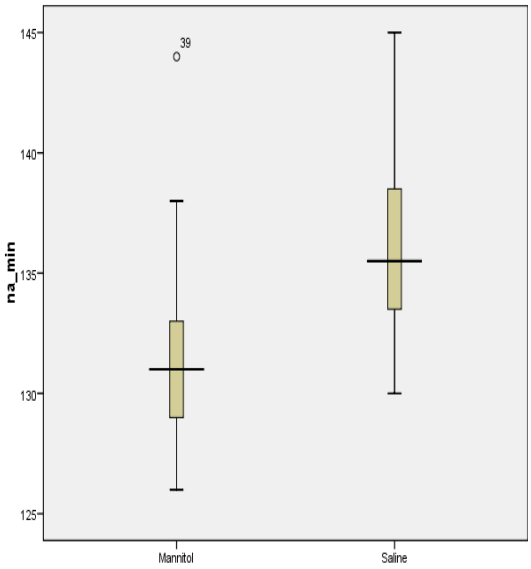


	Hypernatremia	coagulopathy	Dehydration	Pulmonary edema	Hemolysis	Renal failure	Shock	SAH
Mannitol	0	4	11	2	0	2	11	0
Saline	6	9	4	1	1	4	3	1
p - value	0.026	0.225	0.045	1	1	0.67	0.03	1

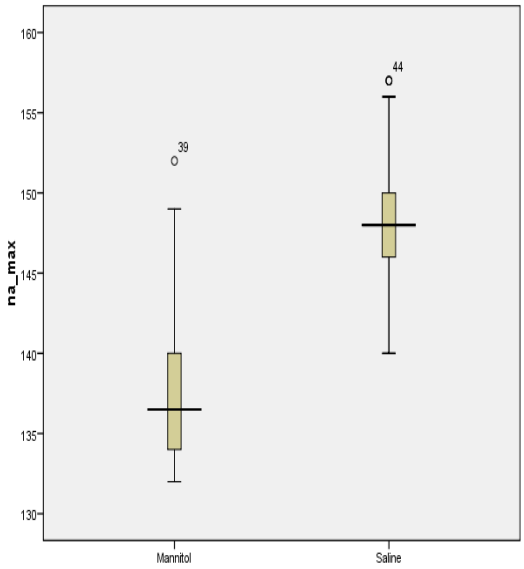
- Dehydration and shock were significantly higher in mannitol group.
- Hypernatremia was significantly higher in 3%saline group.

SERUM SODIUM VALUE

Minimum sodium value



Maximum sodium value



- 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 value attained during the study 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.

DURATION OF VENTILATION

		Total ventilation (hrs)	Manual (hrs)	Mechanical (hrs)
Mannitol	Mean	136.88	11.37	127.90
	Range	0 - 648	0 - 103	0 - 648
	Std. Dev	155.19	19.72	152.02
3%Saline	Mean	280.45	15.95	264.00
	Range	0 – 3336*	0 - 236	0 - 3100
	Std. Dev	571.35	37.85	540.38
Total	Mean	208.66	13.66	195.95
	Range	0 - 3336*	0 - 236	0 - 3100
	Std. Dev	422.21	30.07	400.32
p - value		0.06	0.35	0.06

- Mean ventilation duration was 136 hrs in mannitol group (0-648hrs) and 280 hrs in saline group (0-3336hrs). Ventilation duration was not statistically significant between both groups.

* In 3%saline group, one child with TBM was ventilated for 3336hrs (4 ½ months) and this child recovered with neurological sequelae.

OTHER OBSERVATIONS

- CT Brain was taken in 80% of mannitol group and in 72.5% of 3%saline group.

- 52.5% of both groups had features of cerebral edema in CT brain.

DISCUSSION

The earliest description in the literature of the use of osmotic agents dates back to 1919 [*18*]. While studying the transport of salt solutions into the neuraxis, Weed and McKibben observed that intravenous administration of a concentrated salt solution resulted in an inability to withdraw CSF from the lumbar cistern due to a collapse of the thecal sac. This serendipitous observation was followed by an elegant set of experiments in an animal model in which they demonstrated (under direct visualization via a craniotomy) regression of the brain away from the cranial vault with intravenous infusion of hypertonic saline solutions and herniation of brain tissue with administration of hypotonic fluids. This set of observations has formed the basis for osmotherapy. Concentrated urea was the first agent to be used clinically as an osmotic agent. [*8,9,19*]. Its use was short-lived and is of historic interest only because of several untoward side effects (nausea, vomiting, diarrhea, and coagulopathy) [*19*]. The interest in elevating plasma oncotic pressure as a strategy to ameliorate cerebral edema with the use of concentrated human plasma proteins, which appeared briefly in 1940, was short-lived due to several concerns, including cost, short half-life, cardiopulmonary effects, and allergic reactions [*19*]. Glycerol was possibly the second osmotic agent to be

used clinically. Mannitol, an alcohol derivative of simple sugar mannose, was introduced in 1960 and has since remained the major osmotic agent of choice in clinical practice [*8,9,19*]. Its long duration of action (4–6 hours) and relative stability in solution have enhanced its use over the years. The extra osmotic properties of mannitol have been studied extensively and may provide additional beneficial effects in brain injury, including decreases in blood viscosity, resulting in increases in rCBF and CPP, and a resultant cerebral vasoconstriction leading to decreased CBV,[*20,21*] free radical scavenging,[*22*] and inhibition of apoptosis [*23*].

Renewed interest in hypertonic saline solutions reappeared in the 1980s, when they were used in small-volume resuscitation in patients experiencing hemorrhagic shock. [*8,9*]. These studies demonstrated that prehospital restoration of intravascular volume improved morbidity and mortality rates and physiological parameters (such as systemic blood pressure, cardiac index, and tissue perfusion) in this subset of patients [*24*]. In subsequent studies, cerebral effects of these solutions were investigated in well-controlled experimental studies in animal models of acute brain injury. Like mannitol, hypertonic saline also possesses unique extraosmotic properties, including modulation of CSF production and resorption and accentuation of tissue oxygen delivery [*8,9*].

The use of hypertonic saline solution in the treatment of cerebral edema and elevated ICP in the clinical setting is largely based on an extension of laboratory-based research, a few prospective studies in humans, and anecdotal case reports. The first report to demonstrate the efficacy of hypertonic saline in patients with TBI [*25*] involved two patients with elevated ICP refractory to mannitol who were treated successfully with a single intravenous bolus of 30% saline, after which ICP decreased and systemic perfusion improved. Continuous intravenous infusion of 2.5 and 5.4% hypertonic saline enhanced CPP and improved somatosensory evoked potentials after brainstem trauma [*26*]. Likewise, in an uncontrolled, nonrandomized study, [*27*] reductions in ICP were noted with the use of 7.5% hypertonic saline treatment following TBI.

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,[*28*] ICP and intraoperative clinical assessment of brain swelling were similar in both treatment groups.

Most of these study perspectives were from adult population and only few studies were available in pediatric population. In a double-

blind crossover study, in which 3% hypertonic saline for TBI was used in a pediatric population, ICP was reduced by approximately 5 mmHg for 2 hours compared with ICP in patients who required equal volumes of isotonic saline. These available studies have compared population with traumatic etiology which contribute meagrely to cerebral edema in pediatric patients. Only two studies done by Yildizdas., et al and Piyush Upathyay., et al were based 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., (1-120mon) whereas in study by Upadhyay., et al included adolescent population. In our study etiological factors included infective, metabolic, infarct and space occupying lesion. This was comparable with other two studies.

In our study, male population (55-65%) were predominant similar to Upadhyay et al. In the study by Yildizdas et al, female population (52-60%) was predominant. Clinical signs and symptoms in our study were comparable with other studies.

In our study, Glasgow coma scale in the both groups was 6.77±1.352 (3-8) and 6.04±1.51 (4-8). This was higher compared to Yildizdas et al. This was probably because in our study, we recruited

cases without shock. Cases with low GCS tend to have shock and would not have been recruited into the study.

The duration of coma in our study was 59.89±29.67 (mannitol) and 78.91±50.84 (3%saline).This was of shorter duration when compared to study by Yizdizdas et al (123±48.2; 88.6±42.5; 87.5±26.1). In our study, even though duration was higher in 3%saline group, this did not attain statistical significance.

In our study, overall mortality, age wise mortality and etiological mortality comparisons were not statistically significant similar to the study by Upadhyay et al. whereas study by Yildizdas et al showed statistically decreased mortality in hypertonic saline group.

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

Complications like dehydration, shock were significantly more in mannitol group and in 3%saline group, hypernatremia was significantly

higher. These complications were similar to other studies [*13,14*]. There was no significant tendency for hemolysis or haemorrhage observed in study.

The disadvantage in our study is the fact that ICP monitoring was not conducted. However clinical efficacy has been compared between two groups by mortality assessment and duration of coma.

SUMMARY

In this prospective randomized control study done at the pediatric intensive care unit, Institute of child health, Chennai, 40 patients each were recruited in both mannitol and 3%saline group for treatment of cerebral edema. The following are the highlights of the study:

a) Age group was between 3 -140 months.

b) Gender distribution showed slight male preponderance.

c) Etiology was similar in both groups; infection being the predominant underlying cause.

d) GCS was similar in both groups.

e) Clinical signs and symptoms were comparable between both groups.

f) Duration of coma didn't reveal statistically significant difference between the groups.

g) Overall mortality, age wise and etiology wise mortality were similar between the groups.

h) Shock and dehydration was significantly more in mannitol group

i) Hypernatremia was significantly higher in 3%saline group.

CONCLUSION

To conclude, in the treatment of cerebral edema of infectious, metabolic and non traumatic origin in children, 3%saline is as effective and safe as mannitol.

RECOMMENDATION

3% saline being as effective and safe as mannitol, we need further research on the following issues related to 3%saline in the treatment of cerebral edema:

- The target serum sodium value.
- The duration of treatment of 3%saline.
- The preferable mode of administration, either 3%saline bolus or continuous infusion.

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ABBREVIATIONS

GCS	–	Glasgow coma scale
HTS	–	Hypertonic saline
SPSS	–	Statistical Package For Social Sciences
DKA	–	Diabetic Ketoacidosis
CT	–	Computerised Tomography
THAM	–	Trihydroxy amminomethane
CBF	–	Cerebral Blood Flow
ICP	–	Intracranial pressure
MRI	–	Magnetic Resonance Imaging
CSF	–	Cerebrospinal fluid
PICU	–	Pediatric Intensive Care Unit
TBI	–	Traumatic Brain Injury
CPP	-	Cerebral Perfusion Pressure
CBV	-	Cerebral Blood Volume
DEM	-	Dolls Eye Movement
SIADH	–	Syndrome of inappropriate antidiuretic hormone secretions

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CBV	-	Cerebral Blood Volume
DEM	-	Dolls Eye Movement
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