## Original Articles

# Hypertonic Saline Treatment in Children with Cerebral Edema

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*Objective: To compare the efficacy and side effects of hypertronic saline and mannitol use in cerebral edema. Design: Retrospective study. Setting: Pediatric intensive care unit. Subjects: 67 patients with cerebral edema. Methods: Patients with cerebral edema treated with either mannitol or hypertronic saline (HS) (Group II: n = 25), and both mannitol and HS (Group III: n = 20) were evaluated retrospectively. Cerebral edema and increased intracranial pressure were based on the clinical and/or radiological (CT, MR) findings. When treating with both mannitol and HS (Group IIIA), if patients serum osmality was greater than 325 mosmol/L, mannitol was stopped and patients were treated with only HS (Group IIIB). All patients were closely monitored for fever, pulse, blood pressure, central venous pressure (CVP), oxygen saturation, volume of fluid intake and urine output. Mannitol was given at a dose of 0.25-0.5 g/kg while the hypertonic saline was given as 3% saline to maintain the serum-Na within the range of 155-165 mEq/L. Results: There was no statistically significant difference in terms of Glasgow coma scale, age, gender, and etiologic distribution between the groups. And also distribution of the other treatments given for cerebral edema is not significant. 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 A/B. Patients who received only HS were subdivided according to their serum Na concentrations into 2 groups as those between 150-160 mEq/L and those between 160-170 mEq/L. The duration of comatose state and mortality was not different in patients with serum-Na of 150-160 mEq/L and in patients with 160-170 mEq/L in the hypertonic saline receiving patients. Four patients in the group II developed hyperchloremic metabolic acidosis and 2 patients in the group I had hypotension. As two patients in group II had diabetes insipidus and one patient had renal failure in group I, the treatment was terminated. The causes of death were septic shock, ventilator associated pneumonia with acute respiratory distress syndrome, progressive cerebral edema and cerebral edema with pulmonary edema. Multivariate analysis showed that age, gender, cause of cerebral edema, electrolyte imbalance, hyperglycemia and hyper-ventilation had no significant impact on outcome. Conclusions: Hypertonic saline seems to be more effective than mannitol in the cerebral edema.*

**Key words:** *Cerebral edema, Hypertonic saline, Mannitol.*

Hyperosmolar treatment is one of the important methods for treating cerebral edema, and has been employed since early 1960(1). Urea, glycerol and mannitol were used to treatment of this condition in the early years, but then urea and glycerol were soon abandoned because of low efficacy. Mannitol is still used extensively. Side effects like rebound effect, serum electrolyte imbalance and hypovolemia have led to the continued search for other osmotically active agents. One of them is hypertonic saline.

Studies using isotopic techniques and ion selective microelectrodes have shown that the blood-brain barrier (BBB) is impermeable to sodium (Na) and chloride (Cl) ions with the reflection coefficient for Na and Cl determined to be 1.0 and 0.9 for mannitol(2-4). It has been shown that both in animals with and without intracranial pathology, hypertonic saline (HS) reduces brain water content(5,6) and in traumatized animal models it has more favorable results than mannitol(7,8).

We have been using 3% hypertonic saline in patients with cerebral edema since 2002. In this retrospective study, we aimed to show the effects of hypertonic saline in children with cerebral edema and to compare this treatment modality with mannitol in terms of efficacy and side effects.

**Subjects and Methods**

Patients with cerebral edema treated with either mannitol or HS, and both mannitol and HS in the Pediatric Intensive Care Unit, Çukurova University, School of Medicine between June 2002 and May 2004 were evaluated retrospectively. The patients were divided into 3 groups according to the hyperosmolar agent applied:

*Group I:* Group receiving only mannitol

*Group II:* Group receiving only HS

*Group III:* Group receiving both mannitol and HS. When treating with both mannitol and HS (*Group IIIA*), if patients serum osmality was greater than 325 mosmol/L, mannitol was stopped and patients were treated with only HS (*Group IIIB*)

Cerebral edema and increased intracranial pressure were based on the clinical and/or radiological (CT, MR) findings(9,10). 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. Radiological findings included one or more of the followings: Effacement of the basal cisterns, thin, slit-like or completely obliterated ventricles, obliterated cortical sulci, shift in the midline, and temporal lobe or cerebellar tonsils herniation(9,10). All patients were closely monitored for fever, pulse, blood pressure, central venous pressure (CVP), oxygen saturation, volume of fluid intake and urine output. None of the patients had pulmonary problem. By CVP monitoring, blood pressure, renal function tests, and fluid intake and urine output, every effort was made to keep the intravascular volume within the normal limits; hypervolemia or hypovolemia were avoided. Fluid replacement and maintenence fluid treatment were given to maintain CVP of 5-10 cm $H_2O$. In addition to the hyperosmolar treatment the patients were ventilated to keep the $PCO_2$ at 30-35 mmHg for a period 48-72 hours. Intracranial pressure monitoring could not be applied to any patient. All patients were given midazolam (in a dose of 0.1 mg/kg/h, increased as needed) for sedation and fentanyl (in a dose of 1 $\mu$g/kg/h, increased as needed) for analgesia. Patients were treated with the neuromuscular blocking agent vecuronium (0.1 mg/kg), if there was patient- ventilator asynchrony even

on midazolam and fentanyl infusion. 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. 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. Hypertonic saline was applied both as an infusion and in bolus form. The infusion rate was 0.5-2 mL/kg/h and each bolus was applied as 1 mL/kg for 15 minutes. Na level and osmality sample were obtained after each bolus and/or one for every 3 hours. At GCS ≥8, cerebral edema treatment was terminated. The serum Na concentration was reduced to the normal range gradually over 2-3 days. If any clinical improvement has not been received in spite of hypertonic saline, mannitol and hyperventilation treatment, we used pentothal infusion (Na-thiopental 5-10 mg/kg loading followed by 3-5 mg/kg/h maintenance).

Complications (Hyperchloremic metabolic acidosis, renal failure, subarachnoid hemorrhage, central pontine myelinosis, coagulopathy disorder, pulmonary edema, hypokalemia and hemolysis) were recorded.

The protocol was reviewed and approved by the local ethics committee of the Faculty of Medicine. Statistical analysis was done by SPSS-10.0 (SPSS, Chicago, IL, USA). Chi-square and t tests were used for independent samples and when necessary Mann-Whitney U tests were performed. Survivors and non-survivors were compared using multivariate analysis to identify variables having a significant association with mortality.

## Results

There were 22 children in Group I. Of these, 9 (41%) were male and 13 (59%) were female and their mean age was 67.9 ± 46.4 (range 1-120) months. Group II consisted of 25 children, 12 (48%) male, 13 (52%) female, whose mean age was 68.4 ± 50.3 (range 2-144) months. Group III had 20 children (10 male and 10 female) with a mean age of 70.5 ± 52.2 (range 5-180) months. There were no statistically significant difference between groups in terms of age (P = 0.5) and gender (P = 0.4). The Glasgow Coma Scale of the patients in groups I, II and III at presentation were 4.4 ± 1.3 (3-7), 4.5 ± 1.1 (3-7), and 4.3 ± 1.3 (3-7), respectively (P = 0.85). All patients received midazolam and fentanyl and 7 patients in Group I, 7 in Group II and 9 in Group III were treated with vecuronium.

The etiologic causes are shown in *Table I*. We could not identify any significant difference among the groups in etiological causes (P = 0.8) (*Table I*). Cranial tomography was performed in all patients, and also MRI was performed in 22 patients. Neither hypothermia nor decompressive craniectomy had to be done in any of patients.

Mannitol was given for a total dose of

**TABLE I–**Causes of Cerebral Edema in various Groups

| Etiology | Group I (n = 22) | Group II(n = 25) | Group III(n = 20) |
| --- | --- | --- | --- |
| Meningoencephalitis | 9 (40%) | 10 (40%) | 9 (45%) |
| Hypoxic ischemic encephalopathy | 4 (18%) | 6 (24%) | 4 (20%) |
| Intracranial hemorrhage | 4 (18%) | 5 (20%) | 3 (15%) |
| Meningitis | 2 (9%) | 2 (8%) | 2 (10%) |
| Metabolic encephalopathy | 3 (15%) | 2 (8%) | 2 (10%) |

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. The highest serum Na and osmolarity levels during mannitol, hypertonic saline, and HS + mannitol (Group III subgroup A and B) infusions are shown in *Table II*. Although there was no statistically significant difference in the highest serum Na and osmolarity levels of the groups (P = 0.8, P = 0.5, respectively); duration of comatose state (*Table II, Fig 1*) and mortality rate (*Table II*) were significantly

lower in Group II and Group III A/B. Of 67 patients, 46 survived and 21 (31.3%) died. The causes of death were septic shock (Group I = 2, Group II = 2, Group III = 1), ventilator associated pneumonia with acute respiratory distress syndrome (Group I = 1, Group II = 1), progressive cerebral edema (Group I = 7, Group II = 2, Group III = 2) and cerebral edema with pulmonary edema (Group I = 1, Group III = 1).

Patients who received only HS were

**TABLE II**–*Highest Serum Na Concentration, Osmolarity, Duration of Comatose State and Mortality Rate Between Groups*

| Parameters | Group I (n = 22) | Group II (n=25) | Group III (n =20) | | p |
|---|---|---|---|---|---|
| | | | A* | B* | |
| Osmolarity (mOsm/L) | 321.5 ± 10.8 (305-40) | 343.8 ± 20.4 (313-74) | 325.0 ± 11.5 (305-37) | 337.6 ± 19.8) (309-37) | 0. 5 |
| Serum-Na(mEq/L) | | 157.5 ± 8.8 (144-176) | 137.5 ± 10.4 (130-150) | 157.3 ± 9.3 (148-175) | 0. 8 |
| Duration of comatose state | 123.0 ± 48.2 (18-196) | 88.6 ± 42.5 (28-138) | 87.5 ± 26.1 (24-144) | 87.5 ± 26.1 (24-144) | 0. 004 |
| Mortality (%) | 50 | 25 | 20 | 20 | 0. 003 |

Subgroup A shows patients who received hypertonic saline and mannitol together.
Subgroup B shows patients who received hypertonic saline after stopping mannitol.
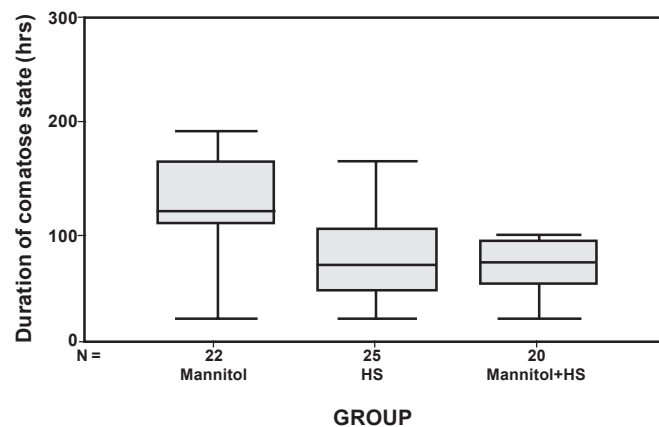


*Fig.1. Duration of comatose state of groups.*

subdivided according to their serum Na concentrations in to 2 groups as those between 150-160 mEq/L and those between 160-170 mEq/L. The duration of the comatose state and mortality rate did not show significant differences between these two groups (P = 0.3, P = 0.4) (*Table III*).

Examination of the patients for possible side effects revealed the following findings: Hyperchloremic metabolic acidosis developed in 4 patients (2 from Group II and 2 from Group III), renal failure developed in one patient from Group I and mannitol had been stopped. In 2 patients, 1 from Group II, 1 from Group III, hypertonic saline treatment was terminated because of diabetes insipidus. No subarachnoid hemorrhage, central pontine myelinosis, coagulopathy disorder, pulmonary edema, hypokalemia and hemolysis were detected during any treatment. Eleven of 21 nonsurvivors and 22 of 47 survivors had hyperglycemia and were treated with insulin. The risk factors for poor outcome were identified by multivariate analysis. This analysis showed that age, gender, cause of cerebral edema, electrolyte imbalance, hyperglycemia and hyperventilation, had no significant impact on outcome (P = 0.2).

## Discussion

For the first time, in 1919, Weed and McKibben[11] 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[12]. 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[13-15]. These experimental findings gave encouragement for application to patients with cerebral edema of traumatic origin. Worthley, *et al.*[16] 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[17-19].

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[20]. Children have been found to tolerate well the rather high serum osmolarity (365 mOsm/L) due to HS[21,22]. Due to its diuretic effect and the consequent risk of development of hypovolemia, mannitol has a greater risk of being complicated by ATN than HS.

**TABLE III**–*Duration of Comatose State and Mortality of Patients According to the Serum-Na Concentration in the Hypertonic Saline Receiving Group*

| Parameter | Serum Na concentration 150-160 mEq/L (n = 25) | Serum Na concentration 160-170 mEq/L (n = 15) | p |
|---|---|---|---|
| Duration of comatose state (hrs) | 80.4 ± 40.1 (24-138) | 91.6 ± 30.2 (28-144) | 0. 3 |
| Mortality (%) | 20 | 27 | 0. 4 |

Comparative studies with mannitol have also been conducted and published. In a prospective, randomized study, Vialet, *et al.*(23) 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.* (24) using 7.5% saline administered as bolus infusion to patients with elevated ICP due to trauma and not responding to the standard treatment showed it to be effective in reducing the ICP and CPP. With the aim of reducing the ICP to below 20 mmHg, Peterson, *et al.*(21) 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 retrospective analysis of two years 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 infection, hemorrhage, anoxia, and metabolic factors. ICP measurement could not be conducted in our study, so treatment continued considering the serum-Na concentration and osmolarity until clinical improvement was achieved. We have shown better results in  Group II and Group III with no significant side effects. The main disadvantage is the fact that our study is retrospective and no ICP measurement was conducted. 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 similiar 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(2-4). Because the reflection coefficient for Na and Cl was 1.0, such a side effect, in saline treatment may not be expected.  To our knowledge, there is no report of HS treatment in edema of anoxic, infectious, and metabolic encephalopathy in the literature.

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.*(21) 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(18-21). 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 form within the cells in 72-96 hours(25-28). So after the termination of HS, serum-Na concentration should be gradually reduced over a period more than 2 days.

Potential side effects of hypertonic saline have been reported(29): Myelinolysis, acute tubular necrosis and renal failure, subdural hematoma or effusion, heart failure, pulmonary edema, hypokalemia, hyperchloremic metabolic acidosis, coagulopathy, intravascular hemolysis, and rebound cerebral edema may occur. Myelinolysis occur more frequently if there is a rapid transition from

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**Key Messages**

- Hypertonic saline treatment is effective and safe in the treatment of infectious,anoxic, hemorrhagic and metabolic origin.

- Serum sodium should be maintained between 150-160 mEq/L while treating with hypertonic saline.

- We recommend bolus dose of 1 mL/kg at 3% saline for 4-6 times in 15 minutes and then infusion dose of 0.5-2 mL/kg/hr.

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hyponatremia to hypernatremia. For myelinolysis to occur a daily serum-Na concentration load of 35-40 mEq/L is required(30). 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. In 6 of our patients hyponatremia was present initially. However, no patient developed daily serum-Na rise exceeding 20-30 mEq/L. MRI study of 22 patients, performed 1-5 days after the termination of saline treatment in group III revealed no signs of pontine myelinolysis. Also, 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. In 4 patients, hyperchloremic metabolic acidosis developed but resolved with proper treatment.

In conclusion, in the treatment of cerebral edema of infectious, anoxic, hemorrhagic and metabolic 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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