Efficacy of Mannitol in the Management of Cerebral Oedema in Hypoxic Ischemic Encephalopathy Stage-II following Perinatal Asphyxia in a Tertiary Level Hospital

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Abstract

Background: The use of mannitol in reducing cerebral edema in case of perinatal asphyxia in Hypoxic Ischemic Encephalopathy Stage-II is considerably contributing.

Objective: To find out the efficacy of mannitol in reducing cerebral edema in Hypoxic Ischemic Encephalopathy Stage-II following perinatal asphyxia.

Methods: It was a prospective observational study done in the paediatric department of Shaheed Suhrawardy Medical College Hospital, Dhaka from September 2016 to February 2017. According to inclusion criteria total 120 neonates were included in this study by purposive sampling. Among them, 60 neonates were selected as case (treated with mannitol) and 60 were taken as control (treated without mannitol). Data were collected in a structured questionnaire.

Results: During the study period a total of 120 patients were studied. In the study group (Group A), 78.33% were delivered by LUCS whereas in Group-B, the figure was 66.6%. The mean birth weight of neonates of these two groups were 1.9 + 0.76 kg and 1.73 + 0.89 kg respectively. PROM, APH, malpresentation, and multiple gestation were statistically significant risk factors in both groups (P=<0.05). About 79.67% neonates of group-A (with mannitol) and 70% of group-B (without mannitol) had radiological improvement following treatment revealing no statistically significant difference (P= >0.05).

Conclusion: From the result of the present study, it can be concluded that there is no significant difference in the management of cerebral edema following perinatal asphyxia with HIE stage-II between the groups treated with mannitol and without mannitol.

Key Words: Perinatal asphyxia, HIE stage-II, Mannitol.

Introduction

The incidence of perinatal asphyxia varies considerably among different countries depending on their level of perinatal care. The World Health Organization (WHO) stated that four to nine million newborns develop perinatal asphyxia each year.1 HIE is a brain injury that prevents adequate blood flow to the infant’s brain occurring as a result of a hypoxic-ischemic event during the prenatal, intrapartum or postnatal period.2 By the age of 2 years, up to 60% of infants with HIE will die or have severe disabilities including mental retardation, epilepsy, and cerebral palsy (CP).3 The incidence of HIE has not declined even with advances in obstetric care (i.e. fetal monitoring) aimed at preventing the hypoxic-ischemic event; thus much of the current neonatal research about HIE focuses on minimizing the extent of subsequent brain injury.4 The treatment of HIE has two dimensions mainly. One is to control convulsion and the next one is to reduce cerebral edema and thus to reduce secondary brain injury. Anticonvulsant drugs are
usually used to control seizure. If cerebral edema can be addressed as early as possible secondary brain injury can be minimized. So, steroid and osmotic agents like mannitol can be used.5

Mannitol is an osmotic agent and intravenous Mannitol is used to induce diuresis in clinical situations, such as cerebral oedema and acute renal failure.6 As an osmotic diuretic, Mannitol is currently recommended for the treatment of cerebral oedema.7 Continual assessment of neurologic status, including ICP monitoring, is required to assess the need for administration of hyperosmolar agents such as Mannitol. Renal function, daily fluid intake output, serum electrolytes, and serum and urine osmolality should be monitored while mannitol is being administered; for treatment of elevated intracranial pressure, serum osmolality should be maintained 310 to <320 mOsm/kg.8 For systemic effect, Mannitol must be given parenterally. It is administered as intermittent bolus doses via central venous access. It has the potential to crystalize and if crystals are present, they have to be dissolved by warming infusion fluids and through a 5-micron in-line filter.9

In neonates with HIE, monitoring and evaluation, outcome prediction and response to the treatment are measured with a combination of a neurologic examination, MRI, and electroencephalography (EEG).10 However, unstable neonates may not tolerate transport for an MRI of the brain or the length of the MRI scanning time. Moreover, hyperthermia therapy may depress the amplitude-integrated EEG (aEEG) and thus limit the early predictive ability of aEEG. Cranial ultrasound (US) is the initial investigation of choice in suspected cases of neonatal HIE as it is in expensive, portable and imparts no radiation exposure. Cranial USG is highly sensitive for detecting intracranialhemorrhage, hydrocephalus, and cystic PVL. Increased resistive index (RI) of the middle cerebral artery (MCA)on Doppler sonography helps to identify severe HIE.11

Methodology:
This was a Prospective observational study conducted in paediatrics department of ShSMCH from September 2016 to February, 2017. According to inclusion criteria 120 patients were included in this study by purposive sampling. They were further divided into two groups; 60 in each group. Randomization was done by taking neonates presenting with inclusion criteria in the hospital in Saturday, Monday, Wednesday, 1st Friday and 3rd Friday as group- A (with mannitol). Neonates presenting with inclusion criteria in the hospital in Sun, Tuesday, Thursday, 2nd and 4th Friday were taken as group- B (without mannitol). group- A (with mannitol) patients received inj. phenobarbitone 20mg/kg/dose as 1st loading dose over 20 minutes followed by 10 mg/kg/dose over 10 minutes as 2nd loading dose (if convulsion not controlled by 1st loading dose) followed by 10 mg/kg/dose over 10 minutes as 3rd loading dose (if convulsion not controlled by 2nd loading dose) then 5 mg/kg/day - 12 hourly as maintenance dose as well as inj. mannitol 1 gm/kg/day once daily for 3 days where group B patients (without mannitol) received only inj. phenobarbitone with same dose schedule. If inj. phenobarbitone did not work effectively to control seizure, then phenytoin inj. was used in 30 mg/kg/dose over 30 minutes as loading dose then 5 mg/kg/day 12 hourly as maintenance dose in both groups. Ultrasonography of brain was done on admission to confirm the presence of cerebral oedema and a repeat ultrasonography of brain was done after 3 days of treatment to see its effect.

The data were collected by the active participation of the patient’s interview by the preformed questionnaire. Data were processed and analyzed with the help of computer program SPSS ( Statistical Package for Social Sciences ) version 16. Quantitative data were presented as mean and standard deviation; and comparison between before and after was done by unpaired “t” test. Qualitative data were presented as frequency and percentage; and were compared by Chi square test if needed or Fisher exact test. Odd ratio (OR) with 95% confidence interval was calculated to determine significance of risk factors. A probability (P) value of <0.05 ( P <0.05 ) was considered statistically significant.

Results:
During the study period, total 120 patients were studied. In study group, 78.33% delivered by LUCS whereas in group-B, the figure was 66.6%. The mean birth weight of neonates in group-A and group-B were 1.9 ± 0.76 kg and 1.73 ± 0.89 kg respectively. PROM, APH, malpresentation and multiple gestation were statistically significant risk factors in both groups (P=<0.05). Lethargy (48.33 VS 51.67), hypotonia (40 VS 35), weak reflex (61.67 VS 55), miosis (38.33 VS 41.67) and seizure (38.33 VS 41.61) are common presentation of group-A and group-B respectively and they were statistically non significant. About 79.67% neonates of group-A (with mannitol) and 70% of group-B (without mannitol) had radiological improvement following treatment. The treatment of both group revealed no statically significant difference (P= >0.05).
Table-I

<table>
<thead>
<tr>
<th>Risk factors</th>
<th>Study group (n=60)</th>
<th>Control group (n=60)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>PROM</td>
<td>24 (40)</td>
<td>21 (35)</td>
<td>&gt;0.05NS</td>
</tr>
<tr>
<td>Prolonged labour</td>
<td>29 (48.33)</td>
<td>31 (51.67)</td>
<td>&gt;0.05NS</td>
</tr>
<tr>
<td>APH</td>
<td>7 (11.67)</td>
<td>11 (18.33)</td>
<td>&lt;0.05S</td>
</tr>
<tr>
<td>PE</td>
<td>11 (18.33)</td>
<td>9 (15)</td>
<td>&gt;0.05NS</td>
</tr>
<tr>
<td>Eclampsia</td>
<td>13 (21.67)</td>
<td>17 (28.33)</td>
<td>&gt;0.05NS</td>
</tr>
<tr>
<td>Malpresentation</td>
<td>4 (6.67)</td>
<td>7 (11.67)</td>
<td>&lt;0.05S</td>
</tr>
<tr>
<td>Multiple gestation</td>
<td>2 (3.33)</td>
<td>1 (1.67)</td>
<td>&lt;0.05S</td>
</tr>
</tbody>
</table>

Table-I shows that antepartum hemorrhage (APH), malpresentation and multiple gestation were significantly more frequent (p=<0.05) among the studied newborns than those in control group.

Table-II

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Cases (with mannitol) (n=60)</th>
<th>Controls (without mannitol) (n=60)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Discharge</td>
<td>43 (72.3)</td>
<td>47 (77.29)</td>
<td>&gt;0.05NS</td>
</tr>
<tr>
<td>DORB</td>
<td>11 (18.33)</td>
<td>8 (14.99)</td>
<td>&gt;0.05NS</td>
</tr>
<tr>
<td>Referred to other hospital</td>
<td>6 (10.67)</td>
<td>5 (9.33)</td>
<td>&gt;0.05NS</td>
</tr>
<tr>
<td>Hospital stay in days</td>
<td>13</td>
<td>11</td>
<td>&gt;0.05NS</td>
</tr>
<tr>
<td>Death</td>
<td>7 (11.67)</td>
<td>9 (15)</td>
<td>&gt;0.05NS</td>
</tr>
</tbody>
</table>

Table-II reveals that hospital outcome following treatment were not statistically significant between the groups.

Table-III

<table>
<thead>
<tr>
<th>Cerebral edema</th>
<th>Study group with mannitol (n=60)</th>
<th>Control group without mannitol (n=60)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Present</td>
<td>13 (20.33)</td>
<td>18 (30)</td>
<td>0.08NS</td>
</tr>
<tr>
<td>Absent</td>
<td>47 (79.67)</td>
<td>42 (70)</td>
<td>0.39NS</td>
</tr>
</tbody>
</table>

Table-III shows after giving mannitol, ultrasonography of brain revealed cerebral edema in 20.3% of cases and 30% of control. The observed differences were not statistically significant.

Discussion:

In this study, important maternal risk factors encountered more frequently among the asphyxiated babies were APH (11.67% vs 18.33%), malpresentation (6.67% vs 11.67%) and multiple gestation (3.33% vs 1.67%) among the cases and controls. All the findings showed statistically significant difference (p=<0.05). These findings are consistent with many other studies. Malpresentation was found to be associated with increased risk in this study like that of Daga AS (Table-1).

Here, lethargy (48.33% VS51.67%), hypotonia (40% VS 35%), weak moro reflex (61.67% VS 55%), miosis (38.33% VS 41.67%), seizure (38.33% VS 41.67%) and comatose (5% VS 1.67%) were the common clinical presentation among the cases and controls respectively.

Out of 60 in each group 20% of group A (with mannitol) and 30%of group B (without mannitol) had seizure following treatment. The clinical improvement of hypoxic-ischemic encephalopathy observed in 40% neonates of group A and 35% neonates of group B. In this study, 11.67% of group A (with mannitol) and 15% of group B (without mannitol) died during treatment (Table-2).

After treatment, radiological improvement occurred in 79.67% of group A (with mannitol) and 70% of group B (without mannitol). The difference were not statistically significant (Table-3).

As there was no significant difference between two groups (with or without mannitol) in the management of cerebral oedema in hypoxic-ischemic encephalopathy stage-II, it could not be inferred that treatment with mannitol is more effective than without mannitol.

Conclusion

From the result of the present study, it can be concluded that there is no significant difference in the management of cerebral edema following perinatal asphyxia with HIE stage-II between the groups treated with mannitol and without mannitol.

Conflict of interest: None

Limitations of the study: This is single blinded, single centered study, duration is short.

Recommendations: From the conclusion of this study it can be stated that use of mannitol is not recommended for better management of cerebral oedema in HIE-II following perinatal asphyxia. A multi centered double blinded study
in the divisional/tertiary hospitals of whole Bangladesh with large sample size can reveal the real picture of mannitol action in HIE.

References