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Original Article

Neurodevelopmental outcome in perinatal asphyxia

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Abstract. Perinatal asphyxia is an important cause of neonatal morbidity and mortality. It might lead to neurologic handicaps in children. To find out the incidence of hypoxic ischemic encephalopathy (HIE) in hospital delivered patients, we studied the correlation between Apgar score HIE stage and neurodevelopmental outcome at one year of age. In this prospective study 93 asphyxiated babies admitted to the neonatal intensive care unit (NICU) during the period of Oct 2012 to Nov 2013 were followed for a period of 1 year. The male to female ratio in HIE was 1.16:1. The incidence of HIE in hospital delivered patients (at Trust Hospital) was 2.2%. Death rate in the NICU was 8.4%. HIE was accounting for 22.4% of total NICU deaths. Head circumference at 1 year was significantly low in HIE patients (especially in HIE III). Seizures were present more frequently in patients with HIE II and HIE III than in HIE I patients. Neurodevelopmental delay was present in 31.2% of patients at the end of 1 year in HIE patients. More number of HIE III patients had developmental delay as compared to HIE I and HIE II. Low Apgar score at 5 minutes and low admission pH were predictors of poor neurodevelopmental outcome. Apgar score at 1 minute was poorly related to neurodevelopmental outcome. It was concluded that the birth asphyxia still remains a major cause of morbidity and mortality during neonatal period.

Keywords: Perinatal asphyxia, hypoxic ischemic encephalopathy, neurodevelopment, outcome

Introduction

Neonatal hypoxic ischemic encephalopathy (HIE) is the term used most frequently to designate the clinical and neuropathologic findings thought to occur in the full term infant following either intrapartum or neonatal asphyxia. Perinatal HIE occurs in one to three per 1000 live full-term births [1]. Perinatal asphyxia is defined as failure to initiate and sustain breathing at birth as per WHO definition [2]. The National Neonatal Perinatal Database (NNPD) defined it as moderate birth asphyxia or an Apgar score of 4-6 at 1 minute of age; or severe birth asphyxia or an Apgar score of 0-3 at 1 minute of age [3]. It continues an important cause of neonatal morbidity and mortality. Manifestation of HIE seen in 1.5% live births and is responsible for 20% of neonatal deaths as per NNPD [3]. Seizures occur in 50% of patients of HIE II and 100% of patients with HIE III [4]. Forty-eight percent of patients had neurodevelopmental delay in HIE II [5]. Delayed neurodevelopmental outcome was present in 100% of patients with HIE III [6]. Asphyxia during the perinatal period led to the development of ulegyria in children who, as neonates, survived a perinatal insult. The cycle of hypoxia leading to lactate dependent cellular damage is likely causal in brain damage. As the cells swell with secondary loss of membrane transfer integrity, ischemia simultaneously, cardiac muscle is being affected, resulting in decreased cardiac output and further hypo-perfusion [7]. The outcomes of HIE are devastating and permanent, making it a major burden for the patient, the family, and society.

The aim of this study was to find out the incidence of HIE in hospital delivered patients and correlation between Apgar score or HIE stage and neurodevelopmental outcome at one year of age.

Materials and Method

All term infants admitted in neonatal intensive care unit (NICU) of Sher-I-Kashmir Institute of Medical Sciences (SKIMS) Hospital with the diagnosis of HIE I, II and III during Oct 1, 2012 to Oct 31, 2013 (total 13 months) were included in the study.

Exclusion criteria included infants whose examination was not possible during follow up for at least 2 different examinations were excluded from the study. Every patient was assigned a number, Apgar score, HIE stage, number of seizures if present as well as all metabolic parameters were recorded as per the proforma. Values of head circumference, height and weight were plotted in NCHS Charts104 Anthropometry. They were called back between 1 and 6 months once, and then 2 monthly until one year. On follow up, through

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examination was done and development was assessed by Trivendrum Developmental Screening Chart. Those who didn't turn up were repeatedly contacted.

All children were managed in NICU at SKIMS Hospital, and they were called on follow up at High Risk Clinic for neurological examination. All those who developed even a minor deficit were advised for stimulation therapy, physiotherapy as and when required. EEG, MRI, CT scan, USG and BERA was advised whenever indicated ophthalmic examination was performed on discharge and on first follow up and repeated as and when required. All patients were immunized as per national schedules and advised optional vaccination.

Statistical analysis

Statistical analysis was done using SPSS v20 (Chicago, IL) expressing group variables as mean ± standard deviation. Student's t-test was applied to independent samples of continuous variables, and chi-square or Fisher's exact test was used for categorical values. Statistical significance was set at $p < 0.05$.

Results

Total number of deliveries at Trust Hospital were 3000 cases. Sixty-six of the total patients developed HIE-I, II, III after delivery in Trust Hospital. Number of patients with HIE-I, II, III referred to other hospitals were 85 cases. Total number of patients admitted with HIE-I, II, III were 151 cases. Total NICU admissions were 1267 cases. Total deaths were 107 cases. Death due to HIE I, II, III were 24 cases. Total patients discharged with HIE-I, II, III were 127 cases (151 admissions minus 24 deaths). Cases enrolled for follow up were 102 cases with 46 being HIE I, 42 being HIE II and 14 being HIE III. Ninety-three cases were successfully followed for 1 year and included in the study.

Males were 50 and females being 43 cases with 45 being HIE I, 40 had HIE II and 8 had HIE III. Nine patients were lost to follow up out of which 3 belonging to group HIE III died at home as told by relatives on phone interview. One of the probable reason for lower number of female babies could be the biased attitude of the parents towards girl children.

Incidence of HIE at Trust Hospital was 2.2% (66/3000×100). Death Rate in the NICU at SKIMS Hospital, Soura was 8.4% (107/1267×100). Contribution by HIE to total NICU deaths was 22.4% (24/107×100). Overall, mortality in neonates admitted at SKIMS NICU was 8.4% with major causes including sepsis, prematurity and HIE > HIE was responsible for 22.4% deaths. When followed over a period of time (1 year), it was found that head growth was significantly affected HIE I patients as seen by statistically p value ($p<0.0001$). Head growth was affected more in patients with HIE III as it is evident from mean OFC values. Among the 93 neonates included in the study, 28 patients convulsed at any stage from admission to the follow up. Most convulsions occurred during first 3 days of life. Convulsions occurred in all patients, 8 (100%) belonging to group HIE III. Convulsions were more in group II patients, 17 (42.5%) than group I patients, 3 (6.7%). The patients of group I who convulsed were not included in group II because they convulsed after discharging them from ward while on follow up.

There was a statistically significant relation between HIE stage and occurrence of convulsion ($p < 0.0001$). Twenty-nine patients had neurodevelopmental delay in the form of delayed attainment of milestones or abnormal neurological examination at the end of one year. All 8 patients (100%) of Sarnat stage III HIE had neurodevelopmental delay at the end of 1 year while 21 (52.5%) patients of stage II and no patient of stage I were affected during the same period.

There was statistically significant relation between Sarnat stage of HIE and neurodevelopmental outcome at 1 year ($P<0.0001$). Blood sugar and serum calcium were checked at admission, at 24 hours and again at 48 hours. Any patient with symtomatic hypoglycemia <45 mg/dl was treated with 2 ml/kg of dextrose 10% in water. All those neonates with blood sugar <40mg/dl were enrolled as having hypoglycemia. A total of 10 patients at admission were hypoglycemic while as only 2 patients at 24 hours and 1 patient at 48 hours was hypoglycemic.

There was statistically no significant relation between Sarnat HIE Stage and blood sugar at admission, at 24 hours and at 48 hours of life; $p=0.854$; $p=0.905$; $p=0.512$. There was statistically a significant relation between OFC at 1 year and neurodevelopmental outcome ($p=0.0001$). Patients with neurodevelopmental delay were more likely to have lesser OFC (mean OFC=40.52cm) as compared to unaffected patients (mean OFC=45.86cm). APGAR score at 1 minute had statistically no significant relation with neurodevelopmental outcome ($p=0.092$), while Apgar score at 5 minutes had statistically significant relation with neurodevelopmental outcome ($p=0.0001$). Blood pH at admission had statistically significant relation with neurodevelopmental outcome ($p=0.0001$). Patients with lower admission blood pH had poor neurodevelopmental outcome as compared to patients with higher admission blood pH.

Discussion

Perinatal hypoxic-ischemic encephalopathy (HIE) is an important cause of brain injury in the newborn and can result in long-term devastating consequences. Perinatal hypoxia is a vital cause of long-term neurologic complications varying from mild behavioral deficits to severe seizure, mental retardation, and/or cerebral palsy in the newborn. HIE is an important cause of morbidity and mortality in the neonatal period and of cerebral palsy as a late neurologic sequela in the postnatal period. Although intervention is limited and mostly supportive at this time, it is still important to promptly and accurately identify neonates who have sustained a hypoxic-ischemic brain injury to facilitate optimal management

As per NNPD [3] data manifestation of HIE were seen in 1.5% and as per Cloherty frequency of perinatal asphyxia is approximately 1% to 1.5% of live births [8]. Thornberg et al. reported incidence of birth asphyxia in Swedish Population was 0.54% [9]. In the present study,

incidence of HIE in hospital delivered patients at Trust Hospital was 2.2% (66/3000×100) which is comparable to NNPD [3]. Higher incidence in present study compared to national data may be because facilities for continuous antenatal fetal monitoring are not available in most hospitals of the valley.

HIE was responsible for 20% of neonatal deaths as per NNPD whereas the study by Lee et al. in southern Nepal observed that birth asphyxia accounted for 30% of neonatal mortality [3, 10]. As per Lawn et al., birth asphyxia was responsible for 23% neonatal deaths [11]. As per Bang AT et al., birth asphyxia was responsible for 25% neonatal mortality rate in rural Gadchiroli, India [12]. In the present study, asphyxia was responsible for 22.4% (24/107×100) of neonatal deaths which is comparable to studies of NNPD and Lawn et al. [3, 11]. Mortality in the present study was lesser than the mortality found by Lee et al. and Bang et al. [10, 12]. More mortality in Bang et al. study may be because the study was conducted in rural area [12]. Early recognition and management of complications in HIE patients in our NICU was responsible for lesser mortality than other studies. In the present study, it was found that there is a statistically significant relation between HIE and OFC at 1 year of age. There was more decrease in OFC at 1 year of age with increase in stage of HIE. Similar results were found in the study by Mercuri et al. where 53% of neonates with HIE had suboptimal head growth, with a statistically significant relation between HIE and suboptimal head growth [13]. Cordes et al. also found that initial slow head growth in patients with HIE resulted in development of microcephaly [14].

Pisani et al. found seizures in 50% of patients of HIE II and 100% patients with HIE II and in the Begum et al. study seizures were present in 35% patients with birth asphyxia [4, 15]. In present study, seizures were found in 30.1% patients with HIE. Seizures were present in 100 % cases with HIE III and 42.5% patients with HIE II. Seizures were also present in 6.7% cases with HIE I, but all these patients developed seizures during follow up and not during hospital stay. Seizures in our study were less than the other studies and may be due to regular monitoring and better management of patients.

Carli et al. observed that 52% of neonates who suffered birth asphyxia HIE II were normal at the end of 1 year and 48% patients had neurodevelopmental delay ranging from mild to severe delay [5]. As per Robertson et al., the study in which patients with HIE were followed up to 3.5 years, all patients with HIE I were normal while delayed neurodevelopmental outcome was present in 21.3% of patients with HIE II and 100% patients with HIE III [6]. The results in the present study were comparable with the study of Carli et al. with neurodevelopmental delay present in 52.5% patients with HIE II [5]. But in the present study outcome in patients with HIE II was delayed in 52.5% as compared to patients with HIE II in study by Robertson et al. (21.3%). This can be explained because in our study there was shorter follow up time [6].

In the present study, no significant relation was found between HIE and hypoglycemia. This is in contrast to the study made by Bassu et al. who found that mean blood glucose was significantly lower in asphyxiated patients than in non-asphyxiated neonates [16]. Different results in present study may be attributed to strict blood sugar monitoring during admission. On the other hand, Nadeem et al., while studying relation between hypoglycemia and neurodevelopmental outcome in HIE patients, found that 83.8% of patients were normoglycemic while in our study 89.2% were normoglycemic [17]. Dong et al. studied the relation between birth asphyxia and hypocalcemia [18]. No significant relation was found between the two. In the present study also no significant relation was found between HIE and hypocalcemia.

In the present study, there was a statistically significant relation between OFC at 1 year and neurodevelopmental outcome ($p<0.0001$). Patients with neurodevelopmental delay were more likely to have lesser OFC (mean OFC = 40.52cm) as compared to unaffected patients (mean OFC = 45.86cm). OFC at admission had poor relation with neurodevelopmental outcome at one year of age. Similar results were found by Mercuri et al., who found that suboptimal head growth at 1 year was significantly associated with pattern of brain lesion and neurodevelopmental delay in patients with HIE [13]. Also in the study by Coronado et al., it was found that minimum head circumference and head circumference drop were relevant markers of neurological impairment [19]. In Misra et al. study, there was delayed neurodevelopmental outcome in patients with low Apgar scores at 5 and 10 minutes [20]. Also there was not a significant relation between Apgar score at 1 minute and neurodevelopmental outcome. Ehrenstein et al. found that a five-minute Apgar score < 7 has a consistent association with prevalence of neurologic disability and with low cognitive function [21]. In the present study, results were comparable to studies by Misra et al. and Ehrenstein et al. [20, 21].

In our study, no significant relation was found between Apgar score at 1 minute and outcome whereas a significant relation was found between Apgar score at 5 minutes and neurodevelopmental outcome. Relation between Apgar score at 10 minutes and outcome was not studied. In the present study, we found a statistically significant relation between blood pH at admission and neurodevelopmental outcome in HIE patients at 1 year of age. Mean blood pH at admission in affected patients was lower than the unaffected patients. Graham et al. also found a significant relation between neurological morbidity and blood pH at birth in patients with HIE. Gemma et al. also found that low arterial cord pH showed strong, consistent, and temporal associations with clinically important neonatal outcomes [22, 23].

Conclusion

Birth asphyxia still remains a major cause of morbidity and mortality during neonatal period in India. Overall mortality was 22.4%, which clearly indicates the need for early detection of maternal risk factors, better obstetric

management and the prompt resuscitation measures.

Conflict of Interest

The authors declare no conflicts of interest.

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