Factors associated with adverse neurodevelopment outcome using Bayley III scale at 3 to 6 month follow-up

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Abstract

Introduction: As the survival rate of preterm infants has increased, the management of long-term complications, especially neurodevelopmental impairment, becomes important. Several studies have suggested that adverse neurodevelopment could be induced by systemic inflammation in preterm infants. Preterm infants with systemic inflammation would have impaired neurodevelopment and which biomarkers and neurophysiologic studies during inflammation are associated with poor neurodevelopment. **Objective:** To assess the factors associated with adverse neurodevelopment outcome using bayley iii scale at 3 to 6 month follow-up. **Materials and methods:** This prospective cohort study was conducted in Department of Paediatrics, Mugda Medical College Hospital, Dhaka, Bangladesh from July 2021 to December 2021. After taking informed written consent (annexure-III) from parents of the selected premature infants to participate in the study, a total of 82 neonates were enrolled. Hospitalized inborn and out born babies were included consecutively. **Results:** A total 54 patients were analyzed in 1st follow up visit by using Bayley scale III. Mean cognitive score were 81.67±7.58 and 73.50±10.16 in ACS exposed and ACS unexposed group (p-0.001).Mean language score were 85.33±6.73 vs. 77.88±9.98, (p- 0.002). Mean motor score were 84.50±9.83 vs. 76.83±12.03 in ACS exposed and ACS unexposed group (p- 0.013). Though all scores were below normal in both groups, ACS exposed group had relatively better score than ACS unexposed group at 3 months of age. During 2nd follow up 47 infants were assessed at 6 months of age, mean cognitive score in ACS group was 84.88±12.32 and in ACS unexposed group was 75.71±15.67.which was statistically significant(p-.030).Motor and language composite scores were higher at 6 months in ACS group but no difference between two groups were statistically significant. **Conclusion**: Our prospective cohort study showed that systemic inflammation induced by clinical infection and NEC is associated with poor neurodevelopment in preterm infants. These results may help estimate the neurodevelopmental risk of individual patients who have inflammatory illness and narrow down the target population of neuroprotection in the future.

Introduction

Approximately one-third of preterm survivors suffer from severe long-term neurological disabilities, such as cerebral palsy or mental retardation [1]. The Bayley Scales of Infant and Toddler Development (Bayley-III is the current version) is a standard series of measurements originally developed by psychologist Nancy Bayley used primarily to assess the development of infants and toddlers, ages 1-42 months. This measure consists of a series of developmental play tasks and takes between 45-60 minutes to administer. The test was first published in 1969 by Nancy Bayley [2]. The first two editions of the scales produce 2 scores: the Mental Developmental Index (MDI) was used to assess cognitive and language development, and the Psychomotor Developmental Index (PDI) to assess motor skills. The revised Bayley Scales of Infant and Toddler Development, third edition (Bayley-III, 2006) separated the MDI into distinct cognitive, receptive language, and expressive language scales, and the PDI into fine motor and gross motor scale [2]. Composite Score varies according to institution and country. Most of the study consider composite score > 85-Normal Score 84-70-At risk Score <70-Delayed [3]. In this study score >85 was taken as normal and <85 as 'at risk' or 'delayed'. Data published in 2000 in Pediatrics, which summed up 20 years of antenatal corticosteroid use, demonstrated their safety by reporting no influence on the process of puberty and growth in 12-year-olds who were born preterm and received ACS. Western studies have found antenatal steroid therapy is very effective in preventing

neonatal morbidity, but there is little evidence that ACS affects long-term neurodevelopmental and behavioral outcome in 28- to 32-week survivors [4]. Furthermore, preterm infants carry increased risk of a range of neurodevelopmental impairments and disabilities including behavioral problems, school learning difficulties, and lower growth attainment [5]. Developmental delay in child behavioral outcomes remains an important and adverse complication among low birth weight premature infants. Early recognition of a delay in neurodevelopment implies that early intervention would have beneficial effects on their development..

Materials and methods

This prospective cohort study was conducted in Department of Paediatrics, Mugda Medical College Hospital, Dhaka, Bangladesh from July 2021 to December 2021. The selected premature infants to participate in the study, a total of 82 neonates were enrolled. Hospitalized inborn and out born babies were included consecutively. Newborn whose mother received incomplete dose of antenatal corticosteroids or with congenital anomalies, syndromic manifestations or chromosomal malformations, suspected inborn errors of metabolism were excluded from the study. Death within 24 hours of admission in NICU in both ACS exposed and ACS unexposed group were also excluded. To evaluate development, Bayley Scales of Infant Development III, was administered in a calm environment. In the Bayley III, cognitive development, expressive and receptive language, and fine and gross motor development all were evaluated. Composite scores were analyzed in this study.

This scale was used to assess 5 domains in neurodevelopmental scale, such as: cognitive development, expressive and receptive language, and fine and gross motor development. In this study development classified "normal" if the Bayley III score was above 85 and "at risk/delayed" if the score was below 85 on any of the language, cognitive, or motor scales. Development was classified "normal" if the score is above 85 and "at risk/delayed" if a Bayley III score was below 85 on any of the language, cognitive, or motor scales. In this follow up study, losses of follow up were adjusted by simple mean imputation method. Before each follow up, communication was done with the parents / legal guardian over phone. Patients condition, feeding status, socio economic status, maternal education were assessed and neurodevelopmental status with therapy if needed were advised when came for follow up. The statistical analyses were performed with the use of SPSS version 20.

Results

A total 54 patients were analyzed in 1st follow up visit by using Bayley scale III. Mean cognitive score were 81.67±7.58 and 73.50±10.16 in ACS exposed and ACS unexposed group (p-0.001).Mean language score were 85.33±6.73 vs. 77.88±9.98, (p- 0.002). Mean motor score were 84.50±9.83 vs. 76.83±12.03 in ACS exposed and ACS unexposed group (p- 0.013). Though all scores were below normal in both groups, ACS exposed group had relatively better score than ACS unexposed group at 3 months of age (Figure-1).

During 2nd follow up 47 infants were assessed at 6 months of age, mean cognitive score in ACS group was 84.88±12.32 and in ACS unexposed group was 75.71±15.67.which was

Table 1: *Composite scores of BSID III at 3 months follow up period (n-54)*

BSID III scales	ACS exposed (n- 30)	ACS unexposed (n-24)	P-value
Cognition	81.67±7.58	73.50±10.16	0.001
Motor	84.50±9.83	76.83±12.03	0.013
Language	84.67±6.33	77.88±9.98	0.004

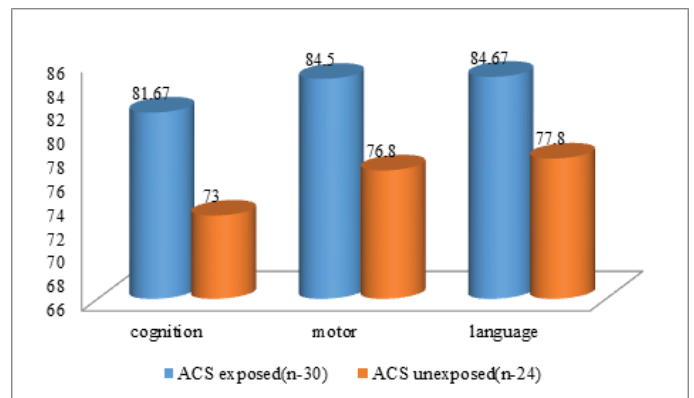Independent t- test for continuous data. P < 0.05 considered as significant.

Figure 1: Mean values of BSID III at 3 months of age in two groups.

Table 2. *Composite score of BSID III at 6 months follow up period (n-47)*

BSID III scales	ACS exposed (n- 26)	ACS unexposed (n-21)	P-value
Cognition	84.88±12.32	75.71±15.67	.030
Motor	87.38±13.18	80.67±12.56	.083
Language	87.00±12.27	80.19±12.67	.069

Independent test for continuous data. P < 0.05 considered as significant

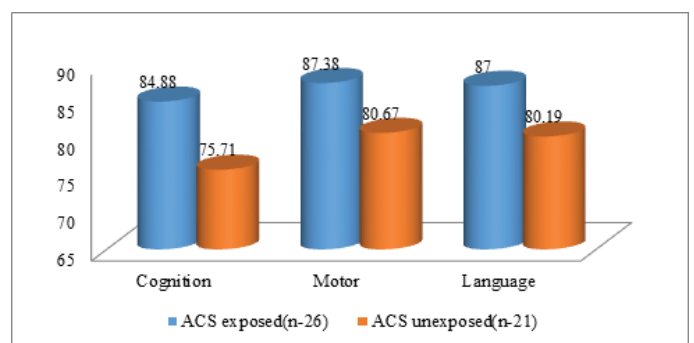*Figure 2. Mean values of BSID III at 6 months of age in two groups.*

statistically significant(p- .030).Motor and language composite scores were higher at 6 months in ACS group but no difference between two groups were statistically significant.

To see the factors associated with adverse neurodevelopment outcome univariate analysis was performed. Only ACS exposure was found to be significantly associated as protective factor for normal neurodevelopment.

Discussion

This prospective cohort study was conducted at the Department of Paediatrics, Mugda Medical College Hospital, Dhaka, Bangladesh from July 2021 to December 2021, illustrates that exposure to antenatal corticosteroids is associated with lower respiratory morbidity and relatively beneficial effect on neurodevelopmental outcomes in infants at gestational ages 34 weeks or less, even after adjustment for multiple significant confounders. This study included 82 premature infants with gestational age ≤ 34 weeks, with history of maternal exposure of ACS and not exposed to ACS. In relation to newborns (Table 3.1) there were no difference between mean gestational age and mean birth weight among two groups. In this study, mean birth weight in ACS exposed and ACS unexposed group were 1665.57±398.53g and 1510.13±377.92g.Mean gestational age were 32.59±1.58 and 31.95±1.59 in ACS exposed and ACS unexposed group. A cross sectional study conducted by Meneguel et al [6], a total 1,051 premature infants were enrolled showing mean birth weight were 1289g and 1290 g among exposed and unexposed groups. Mean gestational age were 31 weeks in both groups. Other recent studies recruited more premature infants with much lower birth weight as their study subjects. A good number of studies have proven significant relationship between very low birth weight infants and development of respiratory morbidities in ACS exposed and unexposed group. Wong D et al [7], and Wang Ya et al [8], between 1999 to 2008 conducted a 10 year retrospective study enrolling 256 infants of ≤ 34 weeks gestation with mean gestational age 29 ± 3.1 and 29.1 ± 2.6 in ACS exposed and ACS unexposed group. Mean birth weight 1147.1 ± 262g and 1199.1 ± 224g among both group respectively. Among the enrolled neonates, 55 (67.1%) cases delivered in this hospital were taken as inborn and 27 (32.9%) cases who delivered outside of this institution, taken as outborn. In our study 77.3% inborn preterm babies received antenatal corticosteroids where as 22.7% out born babies received ACS. This study result reflected that out born cases were more suffered from complications than inborn cases. Because most of the mothers of inborn cases routinely received antenatal corticosteroid during preterm labour, whereas only one third of out born cases received the same. As antenatal corticosteroid is still not a routine practice by doctors in peripheral hospitals and for home delivery by TBA (Trained Birth Attendant).Thus, outborns received incomplete or no ACS in preterm labour. A cluster- randomized trial conducted by Berrueta et al [9] to assess the feasibility, effectiveness, and safety of a multifaceted intervention designed to increase the use of ACS at all levels of health care in LMICs, which showed & lt;10% coverage of ACS in hospital and clinics in low income countries. Overall respiratory distress syndrome and pneumonia also were significantly low in ACS exposed group. Percentage of other cause of respiratory distress like transient tachypnea of newborn and delayed adaptation in

both group were presented in less frequencies in this study. Respiratory supports in any forms were also needed less in ACS exposed group. Duration of respiratory support more than 24 hours was needed more in ACS unexposed group. Studies done by Wang YC, Tseng HI and Joy Christ H showed similar results in which preterm who were born to mothers who have received ACS with gestational age between 24 weeks +6 days and 34 weeks had lesser incidence of respiratory distress syndrome as well as requirement of surfactant and CPAP [8]. Most of the causes were due to sepsis and sepsis related complications.40 neonates in ACS exposed group and 29 neonates in ACS unexposed group were discharged from NICU. 2 infants died before 1st follow up. One was due to road traffic accident and another infant died due to aspiration pneumonia. Total 30 infants in ACS group and 24 infants in ACS unexposed group came for 1st follow up at 3 months of age. BSID III was done to assess neurodevelopmental status by appropriately trained clinical psychologists. Mean composite score were significantly low in ACS unexposed group. Though in ACS exposed group the level did not attained normal. At 6 months of age total 47 infants were followed up. At 2nd follow up language and motor composite domains were improved in ACS exposed group than ACS unexposed group though scores were improved in ACS unexposed group as well. Cognition in both group were low which was statistically significant. Univariate analysis of factor influencing neurodevelopmental outcome shows only ACS exposure acts as significantly protective factor. This study demonstrated that ACS exposure can improve neurodevelopmental outcome at 6 months of age though cognition was low in both group. A prospective study conducted by Naila, et al [10], in Bangladesh included <33 week preterm neonates were assessed at 31 months of age revealed normal development in 32% 45% had mild and 23% had serious neurodevelopmental impairment. Cognition impairment was the most common deficit (60%).This study shows similar result with our study though ACS exposure was not identified. Our study has several strengths. We attempted to capture the point of significant systemic inflammation and conducted a comprehensive evaluation encompassing growth, body fluid biomarkers, neurophysiologic study, brain imaging, and CA of 18 months neurodevelopmental outcomes. We performed Bayley-III, which provides not only granular evaluation of cognitive, language, and motor development, but also social-emotional and adaptive behavior. This has enabled us to examine more diverse aspects of development in study infants.

Conclusion

Our prospective cohort study showed that systemic inflammation induced by clinical infection and NEC is associated with poor neurodevelopment in preterm infants. These results may help estimate the neurodevelopmental risk of individual patients who have inflammatory illness and narrow down the target population of neuroprotection in the future.

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