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Original Research Article

Short Term Neurodevelopmental and Growth Outcomes of Very Low Birth Weight Infants with Neonatal Sepsis in Central India: A Prospective Cohort Study

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Abstract:

Introduction: Sepsis is commonly experienced by infants born very preterm (<32 weeks gestational age and/or <1500 g birth weight), but the long-term functional outcomes are unclear. The long-term outcomes of very low birth infants are influenced by prematurity, as well as the occurrence of various short-term morbidities such as Respiratory Distress Syndrome (RDS), sepsis, Necrotising Enterocolitis (NEC), Patent Ductus Arteriosus (PDA), Intraventricular Hemorrhage (IVH), Paraventricular Leukomalacia (PVL), Retinopathy of Prematurity (ROP), and Chronic Lung Disease (CLD). The objective of this study was to assess Growth Neurodevelopment and outcomes in preterm infants with Neonatal sepsis.

Methods: A prospective cohort study was conducted in the Neonatal Intensive Care Unit (NICU) at NSCB Medical College, Jabalpur, and Madhya Pradesh, India. The duration of the study was one year and six months, from March 2018 to September 2019. A total of 40 very low birth infants were enrolled and followed-up for six months. The infants were divided into two groups: Group1 (<32weeks) and Group2 (>32weeks).Physical parameters such as weight, length, and head circumference were recorded on admission and at one, three and six months of corrected gestational age. Developmental assessment was performed using the Denver Developmental Screening Test-II (DDST-II) method. Laboratory sepsis profile was sent and association of risk factors with Growth and Neuro developmental outcomes was assessed. Data were analysed using Statistical Package for Social Sciences (SPSS) version 20.0 and the Chi-square test, Fisher's-exact test and Student's t-test were used. A p-value less than 0.05 were considered significant.

Result: Among the 40 subjects 12 (30%) were <32 weeks, and 28(70%) were >32 weeks. Overall, parameters were higher in infants >32 weeks. Culture proven sepsis was positive in 25 cases out of which 10 cases have developmental delay. Weight and head circumference, gain velocity were greater in infants 32 weeks during the first three months of life ($p<0.05$). From three to six months, <32 weeks infants showed a significant increase ($p<0.001$) in weight and head circumference gain velocity. The length gain velocity in both groups was comparable since birth, and <32 weeks Very low birth infants demonstrated good catch-up growth, which was statistically significant ($p<0.05$).At six months of corrected age, 16 (40%) infants out of the total 40 infants had abnormal neuro developmental outcomes. A total of 7 (58.33%) of the <32 weeks Very low birth infants and 9 (32.14%) of the >32 weeks VLBW infants had Neuro developmental Delay (NDD). Hypoglycaemia, shock, hyaline membrane disease, and mechanical ventilation were significantly associated with an increased risk of NDD.

Conclusions: Neonatal sepsis in Very low birth weight infants is associated with increased risk of neurodevelopment disability. Due to the paucity of longitudinal follow-up data beyond 6 month, the long-term cognitive effect of neonatal sepsis in very preterm infants could not be conclusively determined. Effects on the development of minor impairment could not be assessed, due to the small numbers of infants included in the studies.

Keywords: Very low birth weight infants, Neuro developmental delay, Neonatal sepsis, Intraventricular hemorrhage, Paraventricular Leukomalacia.

Introduction

Sepsis is a clinical condition characterized by bacteremia and clinical signs of systemic infection [1]. It is one of the events that can occur during neonatal intensive care unit (NICU) admission and contributes significantly to the morbidity of very preterm (VP:<32 weeks gestational age) and/or very low birth weight (VLBW:<1500 g) infants [2–4]. Studies have reported rates of sepsis are inversely proportional to gestational age, with 33% of infants born less than 28 weeks acquiring sepsis compared with 60% of infants born less than 25 weeks [5].

During the neonatal period, complications such as sepsis can have dramatic effects on the growth and development of the child, especially in children born very prematurely [6,7]. The mechanism of how sepsis inflicts brain damage has been hypothesised. Research suggests the developing brain is vulnerable to the systematic inflammatory milieu characteristic of sepsis, as well as cytotoxic and ischaemic injury from hypotension and reduced cerebral blood flow [7]. Together, these factors may result in white matter abnormalities and diffuse injury to premyelinating oligodendrocytes, which have been shown to be closely associated with increased risk for impaired cognitive and motor functioning [8,9].

Many premature infants show significant catch-up growth. The catch- up growth is mostly first noted in the infant's head circumference, which is followed by the infant's weight and length. This usually occurs during the initial two to three years of life and is at its maximum at around 36to40weeks after conception [10]. Premature infants with intrauterine growth retardation without any catch-up growth have a higher risk of NDD and other medical problems than premature infants with a normal growth rate and a significant catch-up growth [11].The long-term outcome of VLBW infants is affected by prematurity, as well as the presence of many short-term morbidities such as RDS, sepsis, NEC, PDA, IVH, PVL, ROP, and CLD [10]. Early identification of these morbidities and efforts to modify the factors associated with these morbidities will help improve the survival of these preterm infants [10].

Materials and Methods

A prospective cohort study conducted at a tertiary level NICU, in the Department of Paediatrics NSCB at Jabalpur, Madhya Pradesh from 01 March 2018 to 30 September 2019.The sample size was estimated using data from the last three years of the NICU, based on the number of VLBW infants with Neonatal sepsis discharged from the NICU of NSCB Medical College Jabalpur, which was approximately 35 infants per year. Ethical clearance was obtained from the Institutional Ethics Committee (No.IEC/2023/4127). Written informed consent was obtained from parents at the time of enrollment of infants

Inclusion criteria: All VLBW babies with neonatal sepsis admitted and discharged from NICU during the study period were included in the study.

Exclusion criteria: Gross congenital malformation, a history of birth asphyxia, dropouts, and those not giving consent were excluded from the study.

Study Procedure

The total number of infants enrolled in the study was 78, out of which 29 were lost to follow-up and 9 infants died after discharge from the hospital. Hence, 40 infants comprised the total sample size of the study [Table/Fig-1].Infants were divided in to two groups :< 32 weeks and >32 weeks and prospectively followed until six months of corrected gestational age. A detailed proforma was filled including details of the neonate and mother. Baseline characteristics including gestational age, mode of delivery, and gender noted. Laboratory sepsis screen was sent and culture sensitivity results were analysed.

Appropriate for Gestational Age/Small for Gestational Age (AGA/ SGA) were noted. Gestational age was recorded based on first-trimester ultrasonography or, if not available, by the date of the last menstrual period. Simple anthropometric measurements such as weight (in kg), length (in cm), and head circumference (in cm) were taken at birth, one month, three months, and six months of corrected age.

Corrected gestational age was calculated from the expected date of delivery of the neonate. Weight was measured using an electronic weighing machine with a precision of 10 grams. Length was measured using an infantometer, and head circumference was measured using a non-stretchable tape. Neuro developmental assessment was done at one, three, and six months using the DDST-II[12]. Infants were labeled as normal if their Development Quotient (DQ) was more than70% in all domains; otherwise, they were labeled as abnormal and referred to the Regional Early Intervention Centre (REIC) located at the Institute.

Risk factors were identified from the case records of infants, and infants at risk were managed according to the protocol [12]. To improve follow-up, periodic reminders were sent to parents through telephone calls. Standard treatment was provided to the infants, and appropriate interventions were made during follow-up when required.

The data was analysed using MS Excel and SPSS version 20.0 for Windows. Categorical variables were tabulated as frequency (n) with percentage (%) distribution, and continuous variables were summarized as mean and Standard Deviation (SD). Student's t-test was used to compare two independent means. The normality test was applied before using parametric tests. Chi-square test and Fisher's-exact test were used to find associations between risk factors and NDD, with a p-value of <0.05 considered significant.

Results

Out of 40 infants, 12(30%) were very preterm VLBW (<32weeks) and 28 (70%) were moderate to late preterm (<32 weeks).

A total of 24 (60%) infants were male, and 16 (40%) were female. Baseline characteristics and anthropometric measurements of the study group are shown in [Table/Fig-2, 3], respectively. All anthropometric parameters of weight gain, length, and head circumference were higher in the >32 weeks VLBW group at six months of corrected gestational age [Table/Fig-3]. Out of the 40 infants studied at the end of six months of corrected age, 16 (40%) infants were found to be abnormal and 24(60%) were found to be normal [Table/Fig-4]. Hypoglycaemia (p=0.021), shock (p=0.007), hyaline membrane disease (p=0.001), mechanical ventilation (p=0.0001), and hyperbilirubinaemia (p=0.004) had a significant association with an increased risk of NDD. A total of 64% of infants with hypoglycaemia, 50% of infants with shock, 73.3% of infants with Hyaline Membrane Disease (HMD), 100% of infants who required mechanical ventilation and 55.6% of infants with hyperbilirubinaemia had abnormal NDD, and this was statistically significant [Table/Fig-5].

Blood Culture was positive in 25 cases out of which 10 babies presented with developmental delay.[Table/Fig-5] Klebsiella pneumonia, Pseudomonas aeruginosa, Escherichia coli, Enterococcus was isolated from blood culture.

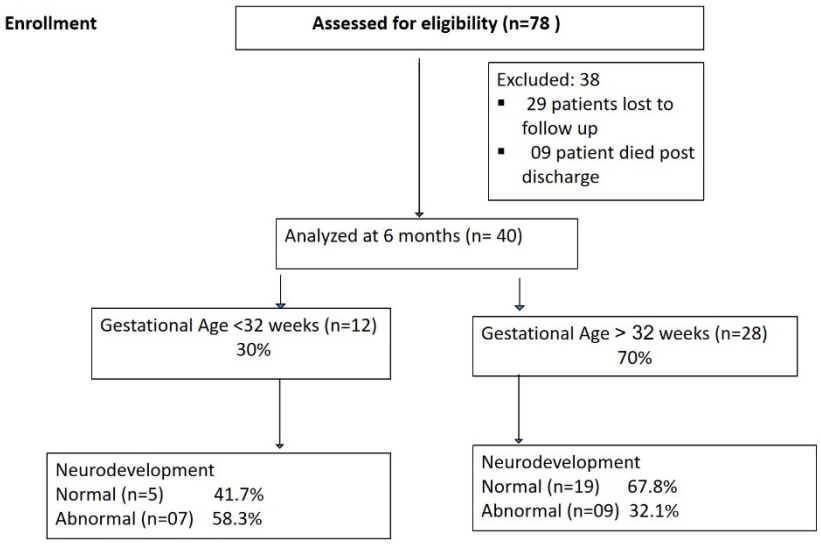

Figure 1: Summary of study participants

Table 1: Baseline characteristics of study groups (n=40) LSCS: Lower segment caesarean section; AGA: Appropriate for Gestational Age; SGA; small for gestational age

Characteristics	Group1	Group2	Total
	<32weeks n (%)	>32weeks n (%)	
Gender			
Male	7(29.2)	17 (70.8)	24
Female	5(31.3)	11 (68.7)	16
Total			40
Gestational age	12(30)	28(70)	40
Mode of delivery			
Vaginal	20 (62.5)	12 (37.5)	32
LSCS	1(12.5)	7(87.5)	8
Total			40
AGA/SGA			

AGA	11 (52.4)	10 (47.6)	21
SGA	1(5)	18(95)	19
Total			40

Table 2: Anthropometric parameters of the two study groups. T test, p value<0.05: significant

Parameters	Group1 (<32 weeks)	Group 2 (>32 weeks)	t-test	p-value
Weight gain(in kg)				
Age (in months)	Mean ±SD	Mean ±SD		
On admission	1.242±0.108	1.368±0.048	5.169	0.0001*
1 month	1.623±0.266	1.970±0.163	5.073	0.0001*
3 months	2.480±0.334	3.192±0.298	6.683	0.0001*
6 months	4.398±0.427	5.110±0.427	4.83	0.0001*
Length gain (in cm)				
On admission	39.51±1.85	42.25±1.14	5.792	0.0001*
1month	43.56±2.39	46.33±1.16	4.965	0.0001*
3 months	49.44±3.01	51.66±1.43	3.178	0.003*
6 months	56.99±4.02	59.97±1.85	3.236	0.003*
Head circumference gain (in cm)				
On admission	29.33±1.69	31.73±0.90	5.842	0.0001*
1 month	30.61±1.95	33.16±0.95	5.578	0.0001*
3 months	34.50±2.19	37.47±0.95	6.038	0.0001*
6 months	38.27±2.78	41.11±0.83	4.263	0.0001*

Table 3: Comparison of neurodevelopment outcome by DDST II at six months of corrected age. Chi-square=2.40, p- value =0.121

Gestational age	Normal n (%)	Abnormal n (%)
Group1 (<32weeks)	5(41.7)	7(58.33)
Group2 (□32weeks)	19 (67.9)	9(32.14)
Total	24(60)	16(40)

Table 4: Association of Neonatal sepsis and other Risk factors with Neurodevelopment Delay (NDD) among study group

Risk factors	N	Developmental delay at six months		Chi-square	p-value
		Normal	Abnormal		
		N (%)	N (%)		
Hyaline membrane disease	15	4(26.7)	11 (73.3)	11.11	0.001*
Sepsis	25	15(60)	10(40)	0	1
Necrotising enterocolitis	12	6(50)	6(50)	0.71	0.398
Hypoglycaemia	14	5(35.7)	9(64.3)	5.29	0.021*
Shock	30	15(50)	15(50)	7.31	0.007*
Ventilation	7	0	7(100)	12.73	0.0001*
Hyperbilirubinaemia	27	12 (44.4)	15 (55.6)	8.38	0.004*
Oxygen requirement	29	15 (51.7)	14 (48.3)	3.01	0.083
Vasopressors	23	13 (56.5)	10 (43.5)	0.27	0.601

Discussion

Infections remain a threat for VLBW-infants, as they are still associated with short-and long-term sequelae and an increased risk of death [13-15, 16]. Our findings concur with previous studies. Fairly recently Ferreira et al. [17] identified clinical sepsis in a Brazilian population as an individual predictor of poorer neuro developmental outcomes. In particular the psycho motoric development seemed to be more affected, as well. Research done by Schlapbach et al. [18] showed proven sepsis to be an individual predictor of poorer neurodevelopment outcomes in infants with EOS and LOS. Before that study, cohorts of Stoll et al. [19] and Bassler et al.[20]had yielded similar results .An association of NDI with culture-proven EOS was shown very recently by Mukhopadhyay et al.[16] on a cohort of extremely preterm infants (gestational age<27weeks) born between 2006 and 2014. Sepsis suspected solely on clinical symptoms, however, did not have a significant association.

Out of 40 babies, 24 (60%) were male. Weight gain velocity was higher in infants born at > 32 weeks from birth up to three months compared to infants

born at <32 weeks, and this difference was statistically significant. Regarding length velocity, both <32weeks and >32 weeks infants showed an increase in length velocity from birth to six months. Infants born at >32 weeks had more head circumference gain from one month to three months, whereas very preterm VLBW infants had more head circumference gain velocity from three to six months. The prevalence of NDD was 20 (50%) at the first month, 18 (45%) at three months, and 16 (40%) at six months of age. In the present study, VLBW infants (<32 weeks) had a significant lag in the growth of all physical parameters at six months of corrected gestational age. These findings are consistent with the observations made by Babson SG, Drillien CM, and Sridhar K et al., [21-23]. The anthropometric parameters in the present study correlated well with the study conducted by Bhargava SK et al., among infants weighing <1500 grams [24]. Although anthropometric characteristics were better at birth in the present study compared to Oliveira MG et al., the final weight, length, and head circumference gains were significantly lower in present study [25]. This difference may be attributed to variations in NICU care conditions.

In the present study, NDD was found in 40% of sepsis cases, which corresponds well with a study by Stoll BJ et al., where NDD was observed in 43% of cases [26].Furthermore, in current study, NDD was found in 64.3% of hypoglycaemia cases. This association is statistically significant and correlates well with a study by Melana N et al., where NDD at six months, assessed using DDSTII, was reported to be 66.6% [27].

There was 50% NDD in NEC cases in present study, which is comparable to Schulzke S Metal., in which NDD was seen in 42.9%of cases [28].In the present study, there was NDD in 50% of cases with shock, and it is statistically significant and correlates well with a study by Chirla DK, in which NDD was found in 50% of cases [29]. In the present study, NDD was found in 55.6% of hyper bilirubinaemia cases. However, jaundice was more often comorbidity in the current study. According to Babu A and Bhat V, significant NDD was found in cases with pathological jaundice [30]. The above studies also indicate that as gestational age and birth weight decrease, the severity and chance of co-morbidity increase, such as RDS, NEC, shock, hypoglycaemia, which contribute significantly to NDD. The lower the gestational age and birth weight, the higher the chances of NDD.

Conclusions

A significant association of Neonatal Sepsis with an increased risk of poor Neuro developmental outcomes in VLBW infants was demonstrated. Measures for earlier detection, prevention, and improved treatment standards have shown a reduction in infections, while the risk of neuro developmental impairment in patients suffering from sepsis seems to be fairly constant. It is difficult to diagnose NDD in infants less than six months of life because very few domains are available for screening. Hence, early screening through frequent follow-up can lead to early detection of at-risk infants for NDD and result in early stimulation therapy and better neuro developmental outcomes.

Ethical Approval –The study was approved by the Institutional Ethics Committee

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