

Research Article

New-born with Hypoglycaemia and their Neurodevelopmental Outcome: A Prospective Study in a Tertiary Care Hospital in Bangladesh

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Abstract

Background: Brain mainly utilizes glucose to maintain its basic function as well as higher order executive functions. Among metabolic problem, hypoglycaemia is the most common in new-born nursery as well as Neonatal Intensive Care Unit (NICU). Hypoglycaemia may adversely affect developing brain and cause neurological impairment.

Objectives: The aim of this study was to assess the neurodevelopmental outcome of new-borns with hypoglycaemia admitted in NICU.

Methods: This prospective observational study was conducted in the department of Neonatology and Institute of Paediatric Neuro-disorder and Autism (IPNA), Bangabandhu Sheikh Mujib Medical University (BSMMU), Shahbag, Dhaka from March 2020 to August 2021. The inclusion criteria were babies admitted in NICU with hypoglycaemia or developed hypoglycaemia. Consent was taken from the parents/guardians whose baby developed hypoglycaemia (blood glucose <2.6 mmol/L). Hypoglycaemia was detected by capillary blood glucose estimation by heel prick tests and confirmed by corresponding blood sugar (RBS). Hypoglycaemia was treated by ensuring feeding or glucose infusion as per standard departmental treatment protocol. New-borns were followed up at 6 and 12 months of age and their neurodevelopmental assessment was done by Bayley Scales of Infant and Toddler Development III (BSID III). Data were analysed using the SPSS 22.0 version software.

Result: Among 66 admitted hypoglycaemic neonates 62 babies neurodevelopmental assessment was done at 6 and 12 months by BSID III method. Among them 48.5% were males while 51.5 % were females, 24.24% were gestational age <34 weeks, 36.36% were between gestational age 34 - <37 weeks and 39.39% were ≥37 weeks of gestation. 60 (90.9%) babies were inborn whereas 6 (9.1%) were out born. Among hypoglycaemic neonates, normal birth weight (≥2500 g) were 27.27%, low birth weight (1500 - <2500 g) were 39.39% and rest of the babies

(33.33%) were < 1500 g. IDM was 42.4% and IUGR was 33.3%. Most patient developed hypoglycaemia within 24 hrs of age (48.55%), among them 13.6% were symptomatic and 46% required glucose infusion. At 1st follow up overall adverse outcome (composite score < 70 in BSID III) were 19.4% and at 2nd follow up overall adverse outcome were 12.9%. Hypoglycaemia with

very low birth weight, hypothermia and symptomatic babies were significantly associated with adverse neurodevelopmental outcome.

Conclusion: Among hypoglycaemic new-borns those were symptomatic, very low birth weight and hypothermic were more prone to develop adverse neurodevelopmental outcome.

Keywords: Hypoglycaemia; Neurodevelopment; Neonates

Abbreviation

BSID: Bayley Scales of Infant and Toddler Development; BSMMU: Bangabandhu Sheikh Mujib Medical University; IRB: Institutional Review Board; NICU: Neonatal Intensive Care Unit; PNA: Perinatal Asphyxia

Introduction

Glucose is the primary source of energy for brain to maintain its basic function as well as higher order executive function. Brain cells (or neurons) need twice as much energy than any other cells in the human body. Hypoglycaemia is the most common metabolic problems seen in the new-born nursery and Neonatal Intensive Care Unit (NICU). Up to 30% of neonates are considered to be at risk for hypoglycaemia and approximately 10% require admission to a neonatal intensive care unit [1]. Incidence of hypoglycaemia is more in premature, Small for Gestational Age (SGA) new-borns, Large for Gestational Age (LGA) and infants of diabetic mothers [2,3]. Neonatal hypoglycaemia is a common disorder that can cause severe neurologic sequelae in neonates, with incidence rates reported range from 0.13% to 0.44% in term and 1% to 5.5% in preterm neonates [4]. Although associations between prolonged symptomatic neonatal hypoglycaemia and brain injury are well established, the effect of mild or asymptomatic hypoglycaemia on neurologic development is uncertain [5,6]. Thus, to determine appropriate glycaemic thresholds for treatment, there have been repeated calls for studies of the effect of neonatal hypoglycaemia on long-term development.

It remains difficult to define neonatal hypoglycaemia using a single glucose value [7]. Lucas, et al., suggested that glucose levels of <2.6 mmol/L found from 3 to 30 days of life in preterm infants may have adverse long-term effects [8]. There are two essential approaches to treating hypoglycaemia in the new-born. The first supports increasing energy intake, orally or intravenously, while the second supports the mobilization of energy stores using counter-regulatory hormones, such as glucagon or corticosteroids [9,10]. Asymptomatic hypoglycaemia includes increasing breastfeeding frequency, supplementing feeds with breast milk or a breast milk substitute, applying intrabuccal dextrose gel, or administering IV glucose [11,12]. Treatment with dextrose gel is inexpensive and simple to administer [13]. Hypoglycaemia may impact brain development. Neonates exposed to hypoglycaemia demonstrate persistent neurodevelopmental and physical deficits [14]. White matter abnormalities including cortical abnormalities, white matter haemorrhage and basal ganglia/ thalamic lesions were found in neuroimaging data. Degree of neurodevelopmental impairment depends on the severity of the white matter injury [15]. Neurological sequelae may present as cerebral palsy, mental retardation, refractory epilepsy, microcephaly, ataxia, loss of vision and learning disability [5,16]. The neurological symptoms of neonatal hypoglycaemia are nonspecific and may present with irritability, tremor, jitteriness, seizures, hypotonia, exaggerated Moro reflex, acute encephalopathy and lethargy. If neurological impairment detected earlier in these vulnerable group, early management can prevent undesirable and often irreversible damage. From previous study it is observed that many of these neurological disabilities caused by hypoglycaemia can be reversible by early intervention. The objective of the study was to identify risk factors of poor neurodevelopmental outcome among hypoglycaemic neonates admitted in NICU.

Methodology

This prospective observational study was conducted in the Department of Neonatology and Institute of Paediatric Neuro-disorder and Autism (IPNA), in Bangabandhu Sheikh Mujib Medical University (BSMMU), Shahbag, Dhaka over a period of 18 months from March 2020 to August 2021. Both term and preterm neonates admitted in the NICU of BSMMU who developed hypoglycaemia were included. New-born delivered with major congenital anomalies, syndromic manifestations and suspected inborn errors of metabolism were excluded from this study. This study was approved by Institutional Review Board.

Study Procedure: All new-borns (inborn and out born) admitted in NICU of this hospital during the study period fulfilling the inclusion and exclusion criteria were enrolled. The parents or guardians were counselled and an informed written consent was

taken from a parent or guardian. Treatment by glucose infusion was given as per standard departmental treatment protocol. Data about maternal history i.e., age, parity, maternal diabetes, HbA1C of mother, pregnancy induced hypertension, eclampsia, maternal risk factor of sepsis like PROM, UTI were collected. Antenatal history regarding periods of gestation, antenatal corticosteroid, birth history and mode of delivery (vaginal/Caesarean/instrumental), as well as information regarding perinatal depression at birth, APGAR score at 1st and 5th minute, any resuscitation required (bag mask/ tactile stimulation) were collected.

Detailed history about gestational age (weeks), birth weight (gram), sex (male/ female), day of onset of hypoglycaemia, either symptomatic or asymptomatic or any other morbidities (jaundice/ sepsis/polycythaemia/hypothermia / NEC / Apnea / PDA / BPD) were also taken. Information regarding the capillary blood glucose level, corresponding venous blood glucose, blood grouping, sepsis screening, treatment history and condition at discharge were collected. For recording all this, a predesigned questionnaire was used.

The new-born who were in risk of developing hypoglycaemia were routinely monitored by capillary blood glucose testing according to departmental protocol. Those had hypoglycaemia by heel prick tests was checked by corresponding blood glucose (RBS) and monitor every 30 - 60 minutes by resident, trained nurse until the glucose level became normal. When two corresponding blood sugar were normal then monitoring was done every 6 hourly. Any symptoms/signs of hypoglycaemia were noted. These new-borns were followed up at 6 and 12 months of age for neurodevelopmental assessment. To assess neurodevelopment, Bayley Scales of Infant and Toddler Development (BSID III) was used. This assessment was done by clinical psychologists assigned from Institute for Paediatric Neurodisorder and Autism (IPNA) and by a trained doctor of NICU, BSMMU, who were blinded about patient's diagnosis. In the BSID III, cognitive, language (expressive and receptive language) and motor (fine and gross motor) development were evaluated. Developmental delay was classified as "delayed" if a BSID III composite score below 70 on any of the subscales. Outcome was recorded as favourable outcome (normal neurologic development, BSID III composite score ≥ 70) and adverse developmental outcome defined as significant delay in one or more developmental domains: cognition, language (receptive and expressive language) and motor functions (fine and gross motor function).

Data Analysis

Data were analysed using the Statistical Package for Social Sciences (SPSS) version 22. Quantitative data were expressed as mean $\pm$ SD and categorical data were presented as proportion/percentage. All quantitative variables (between the groups of favourable and adverse outcome) were compared by unpaired t-test; categorical variables were compared by Chi-square test or Fisher's exact test. Odds ratio (OR) for risk factor was calculated. All the risk factors found to be significant on univariate analysis will be further subjected to multivariate logistic regression analysis. P-value < 0.05 was considered as significant.

Result

During the period of enrolment, total 352 patients were admitted. 72 patients (20%) had hypoglycaemia that were assessed for eligibility. Among them 6 patients were excluded due to major congenital anomaly and death. Finally, 66 patients were included. After discharge of the patient 62 neonate came for Follow up at 6 and 12 months (Fig. 1).

Baseline characteristics of the studied infants are presented in Table 1. Most of the babies were born at term, ≥ 37 weeks of gestation (39.39%). Mean birth weight was 2209.92 ± 808 g. Most of the infants were born by LUCS (97%). About 91% babies were inborn, 42.4% patients were Infant of Diabetic mother and 33.3 % patients were IUGR.

Table 2 showing clinical characteristics of neonatal hypoglycaemia patient. Most patient developed hypoglycaemia within 24 hrs of age of patient (48.5%). Among the hypoglycaemic patient only 9 (13.6%) were symptomatic and 46 (69.7%) patient required glucose infusion.

Among total 62 infants whose outcome in 1st follow up were assessed, 12 patients (19.4%) had adverse neurodevelopmental outcome and rest 50 patients (80.6%) had normal neurologic development (favourable outcome) (Table 3).

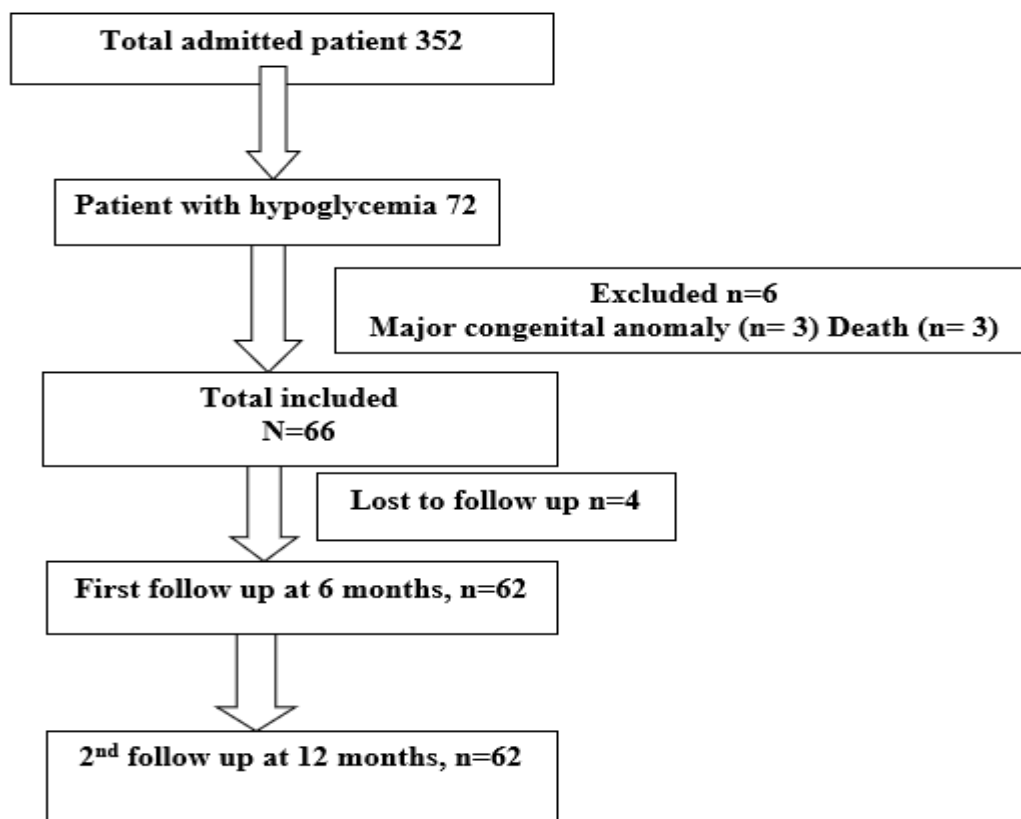


Figure 1: Flow chart of patient enrolment and follow up.

Characteristics	Findings
Gestational age, n (%)	
<34 wk	16 (24.24%)
34 - <37 wk	24 (36.36%)
≥ 37 wk	26 (39.39%)
GA(weeks), mean±SD	35.26±2.95
Birth weight, n (%)	
<1500 gm	22 (33.33)
1500 - <2500 gm	26 (39.39)
≥2500 gm	18 (27.27)
BW(grams), mean±SD	2209.92 ± 808.4
Sex, n (%)	
Male	32 (48.5)
Female	34 (51.5)
Mode of delivery, n (%)	
LUCS	64 (97)
NVD	2(3)
Place of delivery, n (%)	
Inborn	60 (90.9)
Outborn	6 (9.1)
PROM, n (%)	
Yes	6(9.1)
No	60 (90.9)

APGAR score at 5 min	
<7	0
≥7	66(100)
IDM	
Yes	28(42.4)
No	38(57.6)
IUGR	
Yes	22(33.3)
No	44(66.7)
Quantitative data expressed as mean ± SD and categorical data as proportion/percentage. GA: Gestational Age, BW: Birth Weight, LUCS: Lower Uterine Caesarean section, NVD: Normal Vaginal Delivery, SD: Standard Deviation, PROM: Premature rupture of membrane, IDM: Infant of diabetic mother, IUGR: Intrauterine growth restriction.	

Table 1: Baseline characteristics of perinatal factors of hypoglycemic neonates (N=66).

Characteristics	Finding
Age of onset of hypoglycaemia, n (%)	
Day 1	32(48.5)
Day 2- Day7	26(39.5)
>Day 7	8(12.1)
Symptoms n (%)	
Yes	9(13.6)
No	57(86.3)
CBG, n (%)	
2.6 - 1.7 mmol/L	48(72.7)
1.4 - <1.7	12(18.2)
<1.4	6(9.1)
RBS, n (%)	
2.6 - 1.7 mmol/L	30(45.5)
1.4 - <1.7	28(42.4)
<1.4	8(12.1)
Glucose infusion Required, n (%)	
Yes	46 (69.7)
No	20 (30.3)
Infusion duration, n (%)	
6-12 hrs	6(9.1)
13-24	16(24.2)
25-48	6(9.1)
>48	20(30.3)
Sepsis, n (%)	
Yes	24(36.4)
No	42(63.6)
Hypothermia, n (%)	
Yes	14(21.2)
No	52(78.8)
Jaundice, n (%)	
Yes	28(42.4)
No	38(57.6)

PDA, n(%)	
Yes	6(9.1)
No	60(90.9)
BPD, n(%)	
Yes	4(6.1)
No	62(93.9)
All categorical data expressed as proportion/percentage. CBG: Capillary Blood Glucose; RBS: Random Blood Sugar; PDA: Patent Ductus Arteriosus; BPD: Bronchopulmonary Dysplasia	

Table 2: Clinical characteristics of neonates with hypoglycaemia (N=66).

Variable	Outcome
Overall outcome, n (%)	
Adverse (Score, 40 - 69)	12 (19.4)
Favourable (Score, 70 - 160)	50 (80.6)
Cognition	
Adverse (Score, 40 - 69)	6 (9.7)
Favourable (Score, 70 - 160)	56 (90.3)
Language	
Adverse (Score, 40 - 69)	4 (6.5)
Favourable (Score, 70 - 160)	58 (93.5)
Motor	
Adverse (Score, 40 - 69)	10 (16.1)
Favourable (Score, 70 - 160)	52 (83.9)
All categorical data expressed as proportion/percentage.	

Table 3: Outcome of hypoglycaemic neonates in 1st follow up at 6 months of age (N=62).

Comparison of perinatal and clinical characteristic between adverse and favourable outcome at 6 months of age (N=62). Birth weight, infant of diabetic mother, hypothermia, sepsis and symptomatic hypoglycaemia are significantly associated with adverse neurodevelopmental outcome (Table 4-6).

Characteristics	Favourable (N=50)	Adverse (N=12)	P-value
Gestational age, n(%)			
<34 wk	12(75%)	4(25%)	0.724
34--<37 wk	16(80%)	4(20%)	
≥37 wk	22(84.6%)	4(7.7%)	
Birth weight, n(%)			
<1500	10(55.6%)	8(44.4%)	0.002
1500 - <2500	22(84.6%)	4(15.4%)	
≥2500gm	18(100%)	0(0%)	
Infant of Diabetic Mother n(%)			
Yes	28(100%)	0(00%)	<0.001
No	22(64.7%)	12(35.3%)	
Jaundice n(%)			
Yes	18(69.2%)	8(30.8%)	0.05
No	32(88.9%)	4(11.1%)	
Hypothermia n(%)			
Yes	3(42.9%)	4(57.1%)	0.02
No	47(85.5%)	8(14.5%)	

PDA n(%)	4(66.7%)	2(33.3%)	0.32
Yes	46(82.1%)	10(17.9%)	
No			
Sepsis n(%)	8(40%)	12(60%)	<0.001
Yes	42(100%)	00(00%)	
No			
IUGR n(%)	12(66.7%)	6(33.3%)	0.08
Yes	38(86.4%)	6(13.6%)	
No			
Symptomatic or not n(%)			
Yes	1(16.7%)	5(83.3%)	0.001
No	49(87.5%)	7(12.5%)	

Table 4: Comparison of perinatal and clinical characteristic between adverse and favourable outcome of hypoglycaemic neonates at 6 months of age (N=62).

Total 62 infants completed 2nd follow up. Only 8 patients (12.9%) had adverse neurodevelopmental outcome and rest 54 patients (87.09%) had normal neurologic development (favourable outcome).

Variables	Odd Ratio	Confidence Interval (CI)	P -Value
Birth weight	0.18	0.04-0.86	0.02
Hypothermia	.08	0.01-.561	0.010
Symptomatic	.021	0.002-0.232	0.002
Infant of Diabetic Mother	.000	0.000	0.998
Sepsis	958111324.7	0.000	0.997

Table 5: Logistic regression analysis of the association between clinical variables and adverse neurodevelopment of hypoglycaemia infant at 6 months of age.

Variables	Outcome
Overall outcome, n (%)	
Adverse (Score, 40 - 69)	8 (12.9)
Favourable (Score, 70 - 160)	54(87.09)
Cognition	
Adverse (Score, 40 - 69)	0(00)
Favourable (Score, 70 - 160)	62(100)
Language	
Adverse (Score, 40 - 69)	0(00)
Favourable (Score, 70 - 160)	62(100)
Motor	
Adverse (Score, 40 - 69)	8 (12.9)
Favourable (Score, 70 - 160)	54(87.09)
All categorical data expressed as proportion/percentage.	

Table 6: Outcome of hypoglycaemic neonates in 2nd follow up at 12 months of age (N=62).

Comparison of perinatal and clinical characteristic between adverse and favourable outcome at 12 months of age shows birth weight, infant of diabetic mother, hypothermia, sepsis and symptomatic hypoglycaemia were significantly associated with adverse neurodevelopmental outcome and P-value were significant (Table 7).

Characteristics	Favourable (N=54)	Adverse(N=8)	P-value
Gestational age, n(%)			
<34 wk	12(75%)	4(25%)	0.229
34 - <37 wk	18(90%)	2(10%)	
≥37 wk	24(92.3%)	2(7.7%)	
Birth weight, n(%)			
<1500	12(66.7%)	6(33.3%)	0.007
1500 - <2500	24(92.3%)	2(7.7%)	
≥2500gm	18(100%)	0(0%)	
Infant of Diabetic Mother n(%)			
Yes	28(100%)	0(00%)	0.006
No	26(76.5%)	8(23.5%)	
Jaundice n(%)			
Yes	22(84.6%)	4(15.4%)	0.71
No	32(88.9%)	4(11.1%)	
Hypothermia n(%)			
Yes	3(50%)	3(50%)	0.04
No	51(92.7%)	04(7.3%)	
PDA n(%)			
Yes	4(66.7%)	2(33.3%)	0.16
No	50(89.3%)	6(10.7%)	
Sepsis n(%)			
Yes	12(60%)	8(40%)	<0.001
No	42(100%)	00(00%)	
IUGR n(%)			
Yes	14(77.8%)	4(22.2%)	0.21
No	40(90.9%)	4(9.1%)	
Symptomatic or not n(%)			
Yes	3(50%)	3(50%)	0.02
No	51(91.1%)	05(8.9%)	

Table 7: Comparison of perinatal and clinical characteristic between adverse and favourable outcome of hypoglycaemic neonates at 12 months of age (N=62).

Logistic regression analysis both at 6 and 12 months of age shows among hypoglycemic infant those having normal birth weight, normothermia and hypoglycaemia without symptoms are significantly associated with normal neurodevelopmental outcome (Table 5,8).

Parameter	Odd Ratio	Confidence Interval (CI)	P -Value
Hypothermia	0.039	0.005-0.316	0.002
Symptomatic	0.058	0.006-0.532	0.012
Infant of Diabetic Mother	.000	.000	0.998
Sepsis	394456123.4	000	0.997
Gestational Age	0.334	0.126-0.890	0.08
Birth weight	0.148	0.024-.90	0.03

Table 8: Logistic regression analysis of the association between clinical variables and adverse neurodevelopment of hypoglycaemia infant at 12 months of age.

Discussion

Hypoglycaemia is the most common metabolic problem seen in the new-born nursery and Neonatal Intensive Care Unit (NICU). Glucose is the primary source of energy for the brain to maintain its basic functions as well as higher-order executive functions. Poor glycaemic control may be toxic to the developing brain and may cause neurological impairment. Neonatal hypoglycaemia has been associated with various forms of neurological impairment, including developmental delay, seizures, visual processing problems and cognitive difficulties [17-20].

In this study, 62 out of 66 neonates with hypoglycaemia, admitted to NICU and once discharged then followed up at 6 and 12 months of age by detail neurological examination and developmental assessment. To evaluate development, Bayley Scales of Infant and Toddler Development, third edition was used. In the BSID III, cognitive development, expressive and receptive language and fine and gross motor development were evaluated. Developmental delay was classified as “delayed” if BSID III composite score below 70 on any of the subscales. Outcome was recorded as favourable outcome (normal neurologic development, composite score ≥ 70) and adverse developmental outcome defined as significant delay in one or more developmental domains: cognition, language (receptive and expressive language) and motor functions (fine and gross motor function). Among 66 infants 48.5% were males while 51.5 % were females; 16 (24.24%) were gestational age < 34 weeks, 24 (36.36%) were between gestational age 34- < 37 and 26 (39.39%) were ≥ 37 weeks of gestation. Female gender increases the chances of developing hypoglycaemia by three times [21]. In the hypoglycaemia group, adjusted analysis showed a lower fine motor function for boys, $\beta = -16.4$, $p = 0.048$ [22]. But in current study, there was no gender predilection to develop hypoglycaemia and abnormal neurodevelopment. Most of the babies were inborn 60 (90.9%). Mean birth weight of these hypoglycaemic neonates were 2209.92 ± 808.4 , IDM was 28% and IUGR 22%. Almost half of the new-born developed hypoglycaemia within 24 hrs of age (48.55%). Among them 22% were symptomatic and 46% required glucose infusion. Out of 66 hypoglycaemic neonates, 62 have completed both 1st and 2nd follow up at 6 months and 12 months of age respectively. At 1st follow up overall adverse outcome were 19.4% and at 2nd follow up overall adverse outcome were 12.9%. So adverse outcome was decreased at 2nd follow up. Neonatal hypoglycaemia was not associated with increased risk of combined neurosensory impairment (Risk Difference [RD], 0.01; 95% CI, -0.07 to 0.10 and risk ratio [RR], 0.96; 95% CI, 0.77 to 1.21). Prevalence of abnormal neurodevelopmental outcome according to DDST II method was 71.7% [n=28] at 3 months and 66.6% [n=26] at 6 months. Factors such as early onset, symptoms, longer duration of hypoglycaemia, minimum blood glucose level, number of readings < 25 mg/dl and maximum Glucose Infusion Rate (GIR) were significantly associated with adverse outcome [24]. In this study, adverse neurodevelopmental outcome were decreased in subsequent follow up, here factors such as normal birth weight, normo-thermia and hypoglycaemia without symptoms were significantly associated with favourable neurodevelopmental outcome. Plasma glucose abnormalities were not uncommon among full term neonates with sepsis. However, these abnormalities are not associated with morbidity or mortality [25]. Larger studies are needed to confirm these findings. Similar finding was found in our study, showed that hypoglycaemia with sepsis did not increase the risk of adverse neurodevelopmental outcome. We also did not find any significant association of hypoglycaemic infant of diabetic mother with adverse neurodevelopment. This may be due to close monitoring of glycaemic status and other risk in case of Infant of Diabetic Mother (IDM) baby. LBW neonates had a twofold increased risk and VLBW neonates had a fourfold increase in the risk of hypoglycaemia. In current study, normal birth weight baby showed that with increasing birth weight, adverse neurodevelopmental outcome decreases significantly. The association between hypothermia and hypoglycaemia is widely described in different studies. There was a positive correlation of lowest BG level in high-risk neonates of birth weight < 2000 g with their development outcome at 1 year. Although, high-risk infants with BG level ≤ 50 mg% are at added risk for delayed development at 1 year [26]. Infants with early neonatal hypoglycaemia (< 6 h) had a double risk (OR 1.94 [1.30-2.89]) of any neurological or neurodevelopmental outcome and a tripled risk of cognitive developmental delay (OR 3.17 [1.35-7.43]), compared to normoglycemic infants [27]. But in current study temporal association of hypoglycaemia and neurodevelopmental outcome was not evaluated. Hypoglycaemia, both symptomatic and asymptomatic lead to adverse neurodevelopmental outcome as compared to euglycemia though it was worse in symptomatic group [28]. In our study, symptomatic hypoglycaemic new-born were more prone to develop adverse neurodevelopmental outcome than asymptomatic. A recent meta-analysis considering neurodevelopmental outcomes after neonatal hypoglycaemia found a correlation between hypoglycaemic events and an increased risk of visual motor impairment and executive dysfunction in early childhood [29].

Limitations

1. Small sample size due to Covid-19 pandemic situation
2. Single centre study
3. BSID III was not done by single clinical psychologist

Conclusion

Among hypoglycaemic new-borns those were symptomatic, very low birth weight and hypothermic were more prone to develop adverse neurodevelopmental outcome.

Recommendation

All the hypoglycaemic neonate should be followed up to evaluate neurodevelopment outcome. A multicentre with large sample size and longer follow-up study is recommended to see the progression or reversibility of neurodevelopment outcome.

Conflict of Interest

The authors have no conflict of interest to declare.

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