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Original Article

Paediatrics Section

Association between Glycaemia and Neurodevelopmental Outcome at One Year of Age among Term Neonates At-risk for Hypoglycaemia: A Prospective Cohort Study

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ABSTRACT

Introduction: Hypoglycaemia during the newborn period is especially impactful because the brain is dynamically developing. The most common sequelae of hypoglycaemia are disturbances in neurologic development and intellectual function; although minor deficits, especially spasticity, ataxia and seizure disorders, can also occur.

Aim: To assess the association between glycaemia and neurodevelopmental outcomes at one year of age among term neonates at-risk for hypoglycaemia.

Materials and Methods: This prospective cohort study was conducted at the Department of Paediatrics, Mahatma Gandhi Medical College and Research Institute (a tertiary care hospital), Puducherry, India between November 2020 and July 2022. It involved a cohort of neonates at-risk for hypoglycaemia with a gestational age of ≥35 weeks who underwent intermittent monitoring of Blood Glucose (BG) for up to 72 hours of life. The estimated sample size was 146. Assessment at one year included Developmental Assessment Score for Indian Infants (DASII) scores and Amiel-Tison angles, with the assessor being masked to the neonatal glycaemic status.

Results: Of the 146 neonates, 71 were euglycaemic and 74 were hypoglycaemic (57 asymptomatic and 17 symptomatic). The mean birth weights were 2853±0.61 grams for euglycaemic neonates, 2669±0.62 grams for asymptomatic hypoglycaemic neonates and 2965±0.671 grams for symptomatic hypoglycaemic neonates. Three of the 74 hypoglycaemic infants developed cerebral palsy. The mean Motor and Mental Developmental Quotients (MoDQ and MeDQ) were significantly lower at one year in any hypoglycaemic infants compared to euglycaemic infants ($p<0.001$). A BG level of <40 mg/dL demonstrated 98.9% sensitivity for MoDQ and 100% sensitivity for MeDQ, respectively. The Area Under the Curve (AUC) was 0.958 for MoDQ and 0.812 for MeDQ, respectively.

Conclusion: Hypoglycaemia, regardless of whether it is symptomatic or asymptomatic, is associated with poor neurodevelopmental outcomes. All at-risk neonates should be monitored to prevent any episodes of hypoglycaemia.

Keywords: Blood glucose, Infant, Neonates, Neurodevelopmental disorders

INTRODUCTION

Glucose is vital for normal cellular metabolism and serves as the major energy substrate for brain metabolism. The human brain is highly vulnerable to injury when deprived of an adequate supply of glucose. Hypoglycaemia during the newborn period is especially impactful because the brain is dynamically developing. Neonatal Hypoglycaemia (NH) continues to represent a common metabolic issue faced by both healthy and ill-appearing neonates. NH occurs in as many as 19% of infants overall [1] and in up to 51% of infants considered at-risk for NH [2].

The term "at-risk" refers to neonates for whom routine monitoring of BG is recommended. This includes Small for Gestational Age (SGA), Large for Gestational Age (LGA), Infants of Diabetic Mothers (IDM), sick infants (e.g., sepsis, asphyxia, respiratory distress), those who have undergone exchange transfusion, infants on intravenous fluids and parenteral nutrition and infants whose mothers received beta blockers or oral hypoglycaemic agents [3]. Although screening at-risk newborns for NH to avoid adverse outcomes is now standard practice, the dilemma is that not all neonates with low BG levels are symptomatic due to the immaturity of the neonatal brain and other factors that are not well understood. It is essential to maintain BG levels because it is the only nutrient that can be supplied in sufficient quantities to the retina, the germinal epithelium of the gonads and, most importantly, the brain for utilisation as an energy source [4-11].

Current evidence provides a strong correlation between neuroglycopenia (low BG levels in the brain) and subsequent adverse neurologic sequelae [12-22]. The most common sequelae of hypoglycaemia are disturbances in neurologic development and intellectual function, although minor deficits, particularly spasticity, ataxia and seizure disorders, can also occur [13-17]. Thus, assessment and treatment of NH are critically important measures to prevent brain injury.

Over the past several decades, NH has been the subject of extensive discussion, as it represents a preventable cause of cerebral injury and neurodevelopmental deficits [23-25]. However, a universally accepted definition and standardised treatment protocols remain elusive. Therefore, the establishment of clear diagnostic criteria and uniform management guidelines for this prevalent metabolic disorder is critical. Such measures would facilitate the early identification of neonates at-risk, enable the implementation of effective preventive strategies, ensure optimal intervention within the first hours of life and ultimately improve neonatal health outcomes.

Against this background, this prospective cohort study was conducted on term neonates at-risk for hypoglycaemia to investigate the relationship between glucose concentrations and neurodevelopmental assessment at one year.

MATERIALS AND METHODS

The present prospective cohort study was conducted in the neonatal unit, Department of Paediatrics, Mahatma Gandhi Medical College

and Research Institute (a tertiary care hospital), Puducherry, India between March 2021 and December 2022, which included a cohort of term neonates who were at-risk for hypoglycaemia. Approval for the study protocol was obtained from the Institutional Human Ethics Committee (MGMCRI/Res/01/2020/61/IHEC/287).

Inclusion and Exclusion criteria: Neonates born at term who were at-risk for hypoglycaemia (SGA, LGA, IDM and infants whose mothers received beta blockers or oral hypoglycaemic agents) were enrolled after obtaining informed consent from their parents. Neonates with a first episode of hypoglycaemia beyond 72 hours of life, major congenital malformations, severe birth asphyxia, sepsis, ABO and Rh isoimmunisation, grade III or IV Intraventricular Haemorrhage (IVH), or a family history of neurodevelopmental impairment were excluded.

Sample size: The sample size was calculated to be 146 based on the previous study by Yamaguchi K et al., in which the developmental quotient for cases of hypoglycaemia at two years was 103.8±24.2, while for controls, it was 116.8±20.7 [26].

Study Procedure

Term gestation (between 37 and 42 weeks) was confirmed with the expected date of delivery by the first trimester ultrasound report or by the New Ballard score [27]. Growth was categorised as Appropriate for Gestational Age (AGA), Small for Gestational Age (SGA) and Large for Gestational Age (LGA) according to Lubchenco's intrauterine growth chart by plotting the birth weight against the gestational age [28]. SGA is defined as a birth weight <10th percentile, AGA as between the 10th and 90th percentiles and LGA as >90th percentile on the chart. IDM are those neonates born to mothers diagnosed with gestational diabetes or overt diabetes on treatment.

As per the unit protocol, screening for hypoglycaemia commenced one to two hours after birth, then every three to four hours for the first 24 hours and every six to eight hours up to 72 hours of life. These neonates were tested for glucose measurement using glucose test strips. Hypoglycaemia was defined as BG levels <46 mg/dL by strips, confirmed by laboratory glucose [29]. The initial BG was obtained with a Glucometer {Capillary Blood Glucose (CBG)} (Optium Neo H, India), using BG test strips while practicing standard infection control precautions. If the BG level was <50 mg/dL, a Plasma Glucose Level (PGL) test (1 mL of blood collected in a sodium fluoride-containing vacutainer) was performed using the glucose oxidase-peroxidase method on a clinical Sysmos chemistry analyser [29,30].

Depending on the glucose values, the study population was divided into three groups: Those who had normal BG values with strips and one laboratory PGL estimated within the first six hours of life were considered the euglycaemic group; if hypoglycaemia was associated with lethargy, poor feeding, seizures, jitteriness and apnea, they were considered the symptomatic hypoglycaemia group; and those newborns with no listed symptoms were termed the asymptomatic hypoglycaemia group. Birth weight-matched euglycaemic infants were selected for the hypoglycaemic infants and followed-up for one year for outcomes. After discharge, infants were followed-up during immunisation visits for growth and feeding patterns and then at ages six and 12 months for neurodevelopmental assessment. Neurological assessment was conducted using the Amiel-Tison scale [31] and developmental assessment was performed using the Developmental Assessment Score for Indian Infants (DASII) scoring system [32]. The Amiel-Tison scale qualitatively assessed whether hypertonia or hypotonia was present. A diagnosis of cerebral palsy was made with the presence of hypertonia and developmental delay.

The DASII score provides a developmental profile of the infants from 1 to 30 months of age concerning mental and motor development. The mental domain is assessed on 163 items assigned to 10 clusters. The motor development items cover the child's development from supine to erect posture, neck control, locomotion and manipulative behaviour such as reaching, picking up, handling objects and so forth [32].

The DASII scale was administered by a certified tester who was blinded to the neonatal glycaemic status. MeDQ and MoDQ were calculated according to the DASII instruction manual. A score of <70 was considered indicative of a delay, a score between 70-85 was classified as borderline and a score >85 was regarded as average [26]. In the present study, a composite score of <85 was considered indicative of a delay. The primary outcome is neurodevelopmental impairment at one year of age, defined as any of the following findings: MoDQ <85, MeDQ < 85, or abnormal tone (hypertonia/hypotonia) [32].

STATISTICAL ANALYSIS

Quantitative variables were reported as means {Standard Deviation (SD)}, medians {Interquartile Range (IQR)} and qualitative variables as proportions. Comparisons were made using the student's t-test or Chi-square test, as appropriate. A two-tailed significance level of 0.05 was applied for all analyses.

RESULTS

During the study period, 373 term infants were evaluated for eligibility, with 299 classified as euglycaemic and 74 as hypoglycaemic (57 asymptomatic and 17 symptomatic). The overall incidence of hypoglycaemia was 19.7% (74/373). Out of the 299 euglycaemic infants, 150, matched for birth weight, were selected and followed until one year of age for neurodevelopmental assessment. A total of 71 euglycaemic infants and 74 hypoglycaemic infants completed the assessment and were included in the analysis. Among the 74 hypoglycaemic neonates, hypoglycaemia was observed at the following times: 18 (24.3%) infants at one hour, 30 (40.5%) at two hours, 10 (13.5%) at three hours, 11 (14.9%) at six hours and 5 (6.8%) at 12 hours. [Table/Fig-1] depicts the demographic details of the study population. It is evident from this table that the study population was homogeneous in the distribution of birth weight; hence, they were comparable.

Parameters		Euglycaemic group (n=71)	Asymptomatic group (n=57)	Symptomatic group (n=17)	p-value
Gestational age (in weeks) (mean±SD)		38.1±0.913	37.6±0.917	38.1±0.993	0.917
Birth weight (in kilograms)		2.85±0.615	2.66±0.628	2.96±0.678	0.628
Gender	Male	41 (57.8%)	34 (59.6%)	11 (64.7%)	0.940
	Female	30 (42.2%)	23 (40.4%)	06 (35.3%)	
Birth weight category	AGA	33 (46.5%)	33 (57.9%)	10 (58.8%)	0.713
	SGA	28 (39.4%)	19 (33.3%)	05 (29.4%)	
	LGA	10 (14.1%)	5 (87.8%)	02 (11.8%)	
Mode of delivery	Normal	30 (42.3%)	31 (54.4%)	04 (23.5%)	0.079
	Caesarean section	41 (57.7%)	26 (45.6%)	13 (76.5%)	

[Table/Fig-1]: Demographic details of the study population.

The association of tone abnormalities in the symptomatic hypoglycaemia population is depicted in [Table/Fig-2]. A total of 3 infants (15.8%) belonging to the symptomatic hypoglycaemia group, assessed at one year of age, had hypertonia, mental impairment and motor impairment and were diagnosed with cerebral palsy. At one year of age, both the MoDQ and MeDQ were significantly lower in hypoglycaemic infants compared to euglycaemic infants [Table/Fig-3]. The p-values for comparisons of euglycaemia vs. asymptomatic, euglycaemia vs. symptomatic and asymptomatic vs. symptomatic for the MeDQ were 0.001, 0.023 and 0.924, respectively. For the MoDQ, the p-values were 0.001, 0.002 and 0.002, respectively [Table/Fig-4].

Neurodevelopmental impairment		Euglycaemic N=71 n (%)	Asymptomatic hypoglycaemia n=57 n (%)	Symptomatic hypoglycaemia n=17 n (%)
Neuromotor impairment	Hypotonia	0	0	0
	Hypertonia	0	0	3 (15.8%)

[Table/Fig-2]: Neuromotor impairment (tone abnormalities) among the study population.

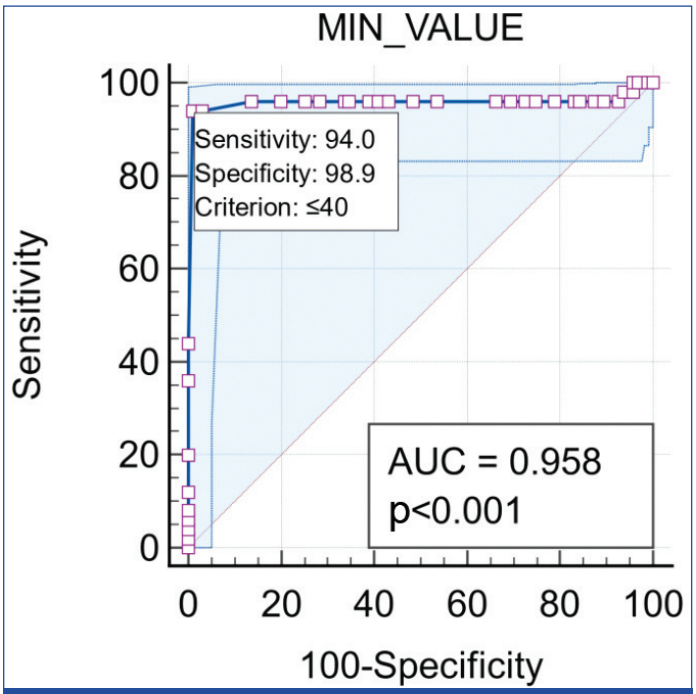
Groups	MeDQ (mean±SD)	MoDQ (mean±SD)
Euglycaemia	91.14±11.82	102.61±8.51
Asymptomatic hypoglycaemia	81.84±11.16	89.49±12.6
Symptomatic hypoglycaemia	81.53±13.75	83.35±11.86

[Table/Fig-3]: MeDQ and MoDQ among the study population.

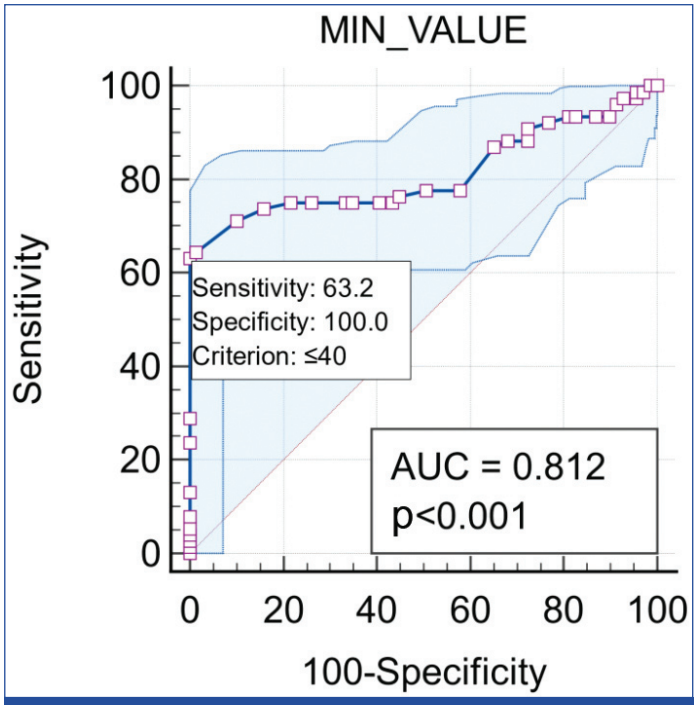
Groups	p-value for MeDQ	p-value for MoDQ
Euglycaemic vs asymptomatic hypoglycaemia	0.0012	0.0012
Euglycaemic vs symptomatic hypoglycaemia	0.0032	0.0022
Asymptomatic vs symptomatic hypoglycaemia	0.924	0.0021

[Table/Fig-4]: Comparison of MeDQ and MoDQ between different groups.
Chi-Square test; (p-value <0.05 is significant

Receiver Operating Characteristic (ROC) curves was constructed to evaluate the relationship between BG levels and MoDQ/MeDQ scores. A BG level of <40 mg/dL showed 94% sensitivity for low MoDQ and 100% sensitivity for low MeDQ. The same glucose value showed 98.9% specificity for low MoDQ and 63.2% specificity for low MeDQ. The AUC for MoDQ was 0.958 (95% CI: 0.911-0.984) and for MeDQ, it was 0.812 (95% CI: 0.739-0.872) [Table/Fig-5,6].



[Table/Fig-5]: ROC curve for MoDQ.



[Table/Fig-6]: ROC curve for MeDQ.

DISCUSSION

The results from the present analysis clearly demonstrate evidence of neurodevelopmental impairment due to hypoglycaemia, irrespective of whether it is symptomatic or asymptomatic. A cut-off glucose value of 40 mg/dL was associated with low mental and motor scores. Published literature has different cut-off values (36-54 mg/dl) to define hypoglycaemia [12,33-35]. The National Neonatology Forum defines hypoglycaemia as a blood sugar level less than 46 mg/dL [33]. However, this level should be viewed with caution in the setting of an infant who is symptomatic with glucose values above cut-off levels. The American Academy of Paediatrics (AAP) in 2011 suggested intravenous fluids only in symptomatic infants with BG levels <40 mg/dL and in asymptomatic infants at BG levels <25 mg/dL within the first four hours of life and <35 mg/dL between 4-24 hours of life, although the effects of asymptomatic hypoglycaemia on neurodevelopmental outcomes were not reviewed [36]. This proposal needs to be re-evaluated, as the present study and supporting evidence from the literature review suggest that any hypoglycaemia causes adverse neurodevelopmental outcomes [37,38].

In the present study, a PGL of 46 mg/dL was set as the cut-off for defining hypoglycaemia. The mean gestational age and birth weight in the hypoglycaemia group were similar to those in the euglycaemic group; hence, we had a homogeneous population for comparison. The number of SGA infants was 28 in the euglycaemic group and 25 in the hypoglycaemic group, respectively. Duvanel CB et al., reported an incidence of 72.9% hypoglycaemia in SGA infants with a similar cut-off as in the present study and found significantly lower scores in psychometric tests at 3.5 and five years of age [39].

Contradictory statements exist from different authors regarding neurodevelopmental outcomes in asymptomatic hypoglycaemia. A study by Koivisto M et al., showed that all 66 asymptomatic hypoglycaemic infants had normal neurodevelopment between one and four years of age [40]. Similarly, Bland PLP et al., did not find any significant low scores in mildly hypoglycaemic infants at four years [41]. Fluge G reported that 71.4% of asymptomatic infants were normal at a mean age of 3.5 years [42]. However, findings in the present study differ, as even asymptomatic hypoglycaemia was associated with significantly lower MoDQ and MeDQ at 12 months when compared to euglycaemic infants. Similar to our observation, Singh M et al., reported that the mental and psychomotor developmental indices were significantly lower in asymptomatic infants with hypoglycaemia [43]. Griffiths AD and Bryant GM found that at 51 months of follow-up, the symptomatic group had a lower DQ than the asymptomatic group [44]. Koivisto M et al., observed that the outcome was worse in the presence of seizures with hypoglycaemia [40].

In the study population, hypoglycaemia occurred within 12 hours of life, with the maximum number of neonates affected in the first and second hours. This may be due to the delayed initiation of breastfeeding. There were no neonates with recurrent hypoglycaemia; hence, the analysis of the impact of the duration of hypoglycaemia on low scores could not be performed. Singh et al., found that the duration of hypoglycaemia was directly related

to the mental developmental index (r= -0.74, y= 102.5-0.69x) and the psychomotor developmental index (r= -0.81, y= 105.6-0.86x) [43]. Similar observations by Fluge G and Lucas A et al., indicated that duration and severity influence adverse neurological outcomes [42,45]. The latter study was conducted on preterm infants.

An ROC curve was created to determine the cut-off level of the lowest BG to predict low DQ scores (DQ < 85), which revealed that low MoDQ and MeDQ were associated with BG levels <40 mg/dL compared to the >40 mg/dL group. Pildes RS et al., showed that infants with asymptomatic hypoglycaemia and BG levels between 20-30 mg/dL did not exhibit poor neurological abnormalities [46], while Singh M et al., found that infants with BG levels of 17.6±4.4 mg/dL had low mental and psychomotor developmental indices compared to those with higher BG [43]. The strengths of the study included that the assessment of neurodevelopmental status was blinded to the neonatal glycaemic status, an adequate sample size with matched euglycaemic controls and the use of the DASII scale, which is an Indian adaptation of the Bayley scale for assessment.

Limitation(s)

The assessment conducted at one year may not correlate with later cognitive outcomes, which is a major limitation. Therefore, it is recommended to have longer follow-ups beyond one year for hypoglycaemic infants to better predict outcomes.

CONCLUSION(S)

The incidence of hypoglycaemia in at-risk neonates was 19.7%. Significantly lower MoDQ and MeDQ were observed among hypoglycaemic infants. All at-risk neonates for hypoglycaemia should be monitored according to institution-derived protocols to prevent any occurrence of hypoglycaemia. Hypoglycaemia is associated with poor neurodevelopmental outcomes, whether it is symptomatic or asymptomatic, compared to euglycaemia.

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