

## Glucose levels in first 3 days and neurodevelopmental outcome at 1 year in low birth weight infants: A cohort study

Ashok Chandrasekaran, P N Suman Rao, Vijaya Raman<sup>1</sup>, Saudamini Nesargi, Chandrakala Bada Shekharappa, Jagdish Prasad Sahoo, Thomas Ranjit, Marie Shalini Chico, Swarnarekha Bhat

From Department of Neonatology, St. John's Medical College and Hospital, <sup>1</sup>Department of Psychiatry, Clinical Child Psychologist, St. John's Medical College and Hospital, Bengaluru, Karnataka, India

**Correspondence to:** Dr. Ashok Chandrasekaran, Department of Neonatology, Sri Ramachandra University, Porur, Chennai - 600 116, Tamil Nadu, India. Phone: +91-9940076527. E-mail: ashokc3681@gmail.com

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### ABSTRACT

**Background:** Definition of neonatal hypoglycemia is still controversial. **Objective:** To find the effect of blood glucose (BG) levels in the first 3 days of life, on developmental outcome at 1 year in low birth weight neonates <2000 g. **Methods:** A prospective cohort study was conducted in tertiary level neonatal intensive care unit and follow-up clinic in south India. Intramural neonates admitted from September 2009 to August 2010 were enrolled. Perinatal and neonatal variables were recorded. Respiratory support, fluids, and feeding management were based on the standard protocols. BG was measured within 2 h, then 6 hourly for 72 h by glucometer and BG <50 mg% was analyzed by hexokinase method. Infants were followed until 1 year corrected age and development age (DA) assessed by Developmental Assessment Scales for Indian Infants (DASII). Motor and mental DA at various BG levels were compared. Composite outcome of motor or mental developmental delay; or cerebral palsy or hearing impairment or visual impairment was analyzed, and logistic regression analysis was performed. **Results:** The mean birth weight and gestation of the study group (n=129) was 1493 g and 32.5 weeks. The 10<sup>th</sup> centile of BG in the first 72 h was 51 mg%. BG below 10<sup>th</sup> centile was seen in 60 infants. The mean motor and mental DA of the infants by DASII assessment at 1 year was 11.3 and 11.5 months, respectively. The motor DA and mental DA were significantly higher until 50 mg% lowest BG level, and positive correlation was seen (r=0.26 motor, 0.2 mental DA). Mean BG level, the presence of symptoms; number of episodes or small for gestation did not influence the DA. The adjusted odds for poor composite outcome when BG was below 51 mg% is 2.83 (0.65-12.3). **Conclusion:** Even though high-risk neonates with BG <51 mg% have a lower motor DA and mental DA at 1 year, than neonates with BG >50 mg%; other morbidities do determine their composite outcome.

**Key words:** Blood glucose, Developmental outcome, Hypoglycemia, Neonate

Hypoglycemia is a common metabolic problem in the neonatal period, but the definition of hypoglycemia is still controversial [1]. Although neuroglycopenic response as increased cerebral blood flow or abnormal evoked potentials is demonstrated in neonates at levels below 30-45 mg% [2,3], there is no defined “safe glucose” level above which there is no risk for developmental delay [4]. Guidelines recommend different cut-offs varying from 25 to 60 mg% for the management of hypoglycemia in neonates without a stringent evidence [1,5-7].

Glucose is primary substrate for brain, especially in infants, to protect brain development [4]. Studies on neurodevelopmental outcomes after neonatal hypoglycemia have conflicting results [8,9]. Several confounders such as gestational age, birth weight, sepsis, respiratory distress, duration of ventilation, asphyxia, intra-cranial bleed, the presence of ductus arteriosus, and socio-economic status influence the outcome of preterm neonate [10,11]. The recent systematic review suggests that

preterm and growth-restricted neonates should be the prime targets for follow-up studies on neonatal hypoglycemia, because of impaired glycogenolysis and gluconeogenesis, and inadequate alternate fuels [10].

This study was conducted in high-risk neonates of birth weight <2000 g, to find the effect of different levels of blood glucose (BG) in the first 3 days of life on their neurodevelopmental outcome at 1 year of corrected age (CA) as assessed by Development Assessment Scale for Indian Infants (DASII).

### METHODS

This prospective cohort study was conducted in a tertiary level neonatal unit in south India. Intramural neonates of birth weight <2000 g born from September 2009 to August 2010 were enrolled for study and eligible infants were followed until 1 year CA in Neonatal Follow-up Clinic (NFC). Prior ethical approval was

obtained. The unit's protocol is to admit and treat neonates of birth weight <2000 g in neonatal intensive care unit (NICU). Parents of eligible neonates were approached soon after admission for consent and enrolment. Neonates with major malformations, severe asphyxia (5 min APGAR <3), meningitis, and severe degree of intra-ventricular bleed were excluded.

Maternal details, including pregnancy complications, and ante-natal steroids were obtained from medical records. Maternal education and details for socio-economic status scale [12] were obtained by a short interview with mother. Gestational age was assessed by first trimester scans (n=42) and last menstrual period (n=87) if early scans were unavailable. Neonates were classified as small, appropriate (10-90<sup>th</sup> centile) and large for gestation based on Lubchenco charts [13].

Respiratory support, surfactant, fluid management, and ongoing care were based on unit's protocol. Duration of ventilation, parenteral nutrition, apnea, blood culture, patent ductus arteriosus (PDA), inotropes, peak bilirubin level, intra-ventricular hemorrhage, necrotizing enterocolitis (NEC), packed cell transfusion, seizures, and chronic lung disease were some of the other variables. Hearing screen, retinopathy of prematurity screen, and thyroid screening reports were noted. Restricted transfusion guideline is the unit's protocol [14]. The cut-off taken for hypoxia, hyperoxia, hypocarbia, and hypercarbia was 50, 100, 25, and 60 mmHg, respectively [15-17].

Neonates were given feeds or intra-venous fluids after admission and BG was measured within 2 h and then 6 hourly. At least 12 measurements were done in the first 72 h. Mean and lowest BG was calculated. Further BG was measured based on unit protocol. Hypoglycemia was managed by standard protocol [18]. Symptomatic neonates or if BG <25 mg%, glucose infusion was started at 6-8 mg/kg/min, following a mini-bolus. If a neonate on fluids had BG <40 mg%, glucose infusion was increased by 2 mg/kg/min. Asymptomatic neonate with BG 25-40 mg% were given feed, and if repeat BG, measured in 30 min was <40 mg%, glucose infusion was started.

BG was measured by Accu-chek active glucometer, which is of ISO-15197 standard [19]. Pre-warmed heel of a neonate was cleaned with spirit and after drying, skin puncture was done in posterolateral aspect by lancet [20]. A good drop of blood touched the edge of glucometer strip and BG was noted. Whenever BG measured by glucometer was  $\leq 50$  mg%, venous blood 0.5 ml was sent to laboratory for "hexokinase" analysis and BG level thus obtained was taken for study [21]. Glucometer measurement and sample collection were done by trained nursing staff or residents on duty.

### Follow-up

Babies were discharged when they had no ongoing problems, weighed  $\geq 1400$  g and gaining weight on paladay or direct feeds. Follow-up in NFC was at least fortnightly to monthly until 3 months CA. All infants received early intervention therapy, iron, calcium, and vitamin supplements. Neuro-motor assessment and development assessments at 3, 6, and 9 months CA were done

by Amiel-Tison and Denver II methods. A total score of  $\geq 5$  was considered abnormal neuro-motor assessment and development delay was considered if infant failed to do any 2 items for age [22,23].

The primary outcome of the study was the developmental assessment by DASII at 12 months of age, which is the Indian adaptation of Bayley Scales [24]. Age placement of the total score gives infant's motor and mental developmental age (DA) in months. Infants who had at least 2 of the 3 visits at 3, 6, 9 months and also completed DASII assessment at 12 months of CA were considered to have adequate follow-up and eligible for analysis. Motor and mental development quotient (DQ) was calculated. Hearing and visual evaluation, done at 8-9 months, were noted. Poor composite outcome was defined by motor or mental DQ below 85% or requirement of hearing aids or impaired vision or cerebral palsy as defined by persistent tone abnormalities.

### Sample Size and Statistical Analysis

Sample size was calculated using nMaster2.0 software. As a pilot study, DASII done at 1 year CA, in 10 infants of birth weight <2000 g showed their mean motor and mental age as  $11.01 \pm 0.71$  and  $11.46 \pm 0.61$  months, respectively. We hypothesized that at CA of 1 year, the DA of infants with low BG levels will be within 0.5 months, when compared to those with normal BG levels. To find a difference of 0.5 months in DA, 63 infants was required in each group at a power 0.8, Type I error 0.05 and two-sided significance.

Statistical analysis was performed using SPSS17.0 for windows. Continuous data were analyzed by t-test when normally distributed or else by Mann-Whitney test. Categorical data were analyzed using Chi-square test or Fisher exact test. Pearson coefficient was used to find a correlation between BG levels and developmental age. Multinomial logistic regression analysis was performed to find the adjusted odds ratio (OR).

### RESULTS

During the period from September 2009 to August 2010, 262 intramural neonates of birth weight <2000 g were admitted to NICU. The details of enrolment and follow-up are as mentioned in trial flow (Fig. 1). Of the 154 infants in follow-up, 129 infants (106 singletons, 23 from twin gestation) had adequate follow-up and eligible for analysis.

The mean birth weight and gestation of 129 infants was  $1493.5 \pm 305.3$  g and  $32.8 \pm 2.5$  weeks, respectively. There were 31 very preterm (<32 weeks), 54 moderate preterm (32-33 weeks), 39 late preterm (34-36 weeks), and 5 were term infants (37-42 weeks) and the majority were appropriate for gestation (76%). Among 1596 BG measurements done by glucometer, 185 readings (11.5%) were  $\leq 50$  mg%, but hexokinase method confirmed only 153 measurements as  $\leq 50$  mg%. The distribution of BG at different ages in first 72 h is shown in Fig. 2. The median number of BG measurements done in a neonate in first 72 h was 12 (range 11-19).

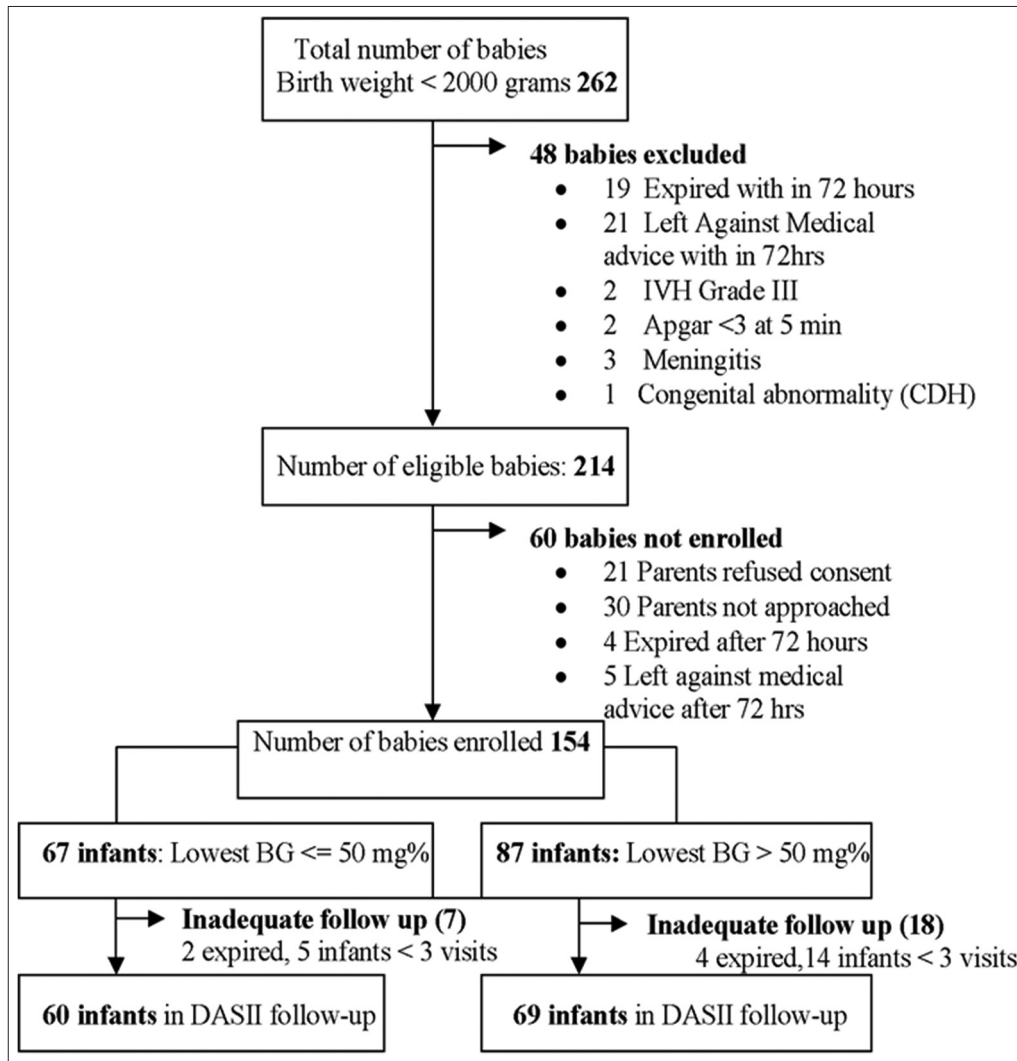


Figure 1: Trial flow – enrollment and follow-up details

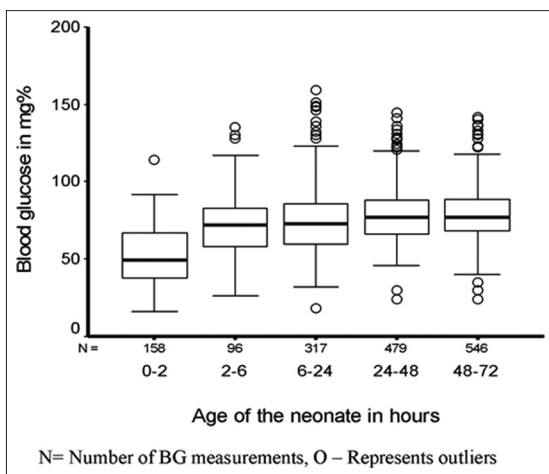


Figure 2: Box-Whisper plot: Blood glucose levels at different ages in first 72 h

Mean BG at 0-2 h was 52.1 mg% and it was significantly lower compared to any other age. 5<sup>th</sup> and 10<sup>th</sup> centile of BG during initial 72 h were 41 and 51 mg%, respectively. Comparison of infants who had BG below 10<sup>th</sup> centile, 51 mg% (n=60) and those who had all BG above 51 mg% (n=69) showed no significant difference

in demographic profile, maternal factors and morbidities of the neonates; except for BG <51 mg% after 72 h, which occurred while tapering intravenous fluids (Table 1). Maternal education level and socio-economic status were also similar in two groups. The median number of episodes of BG <51 mg%, in 60 infants was 3 and 8 infants had BG <51 mg% only in initial screen. Symptomatic hypoglycemia was seen in 13 neonates and the most common symptom was jitteriness followed by lethargy, but none had seizures.

Follow-up at 3, 6, 9 and 12 months CA was done in 115, 119, 117 and 129 infants. At 6 and 9 months CA, abnormal neuro-motor assessment and developmental delay were seen in 19, 25 infants and 22, 17 infants, respectively. Both abnormal neuro-motor assessment and developmental delay at 9 months CA were seen in 12 infants, among them 8 infants had symptomatic hypoglycemia. The mean weight and head circumference at 1 year CA was 8.5±0.78 kg and 44.2±0.5 cm, respectively. The mean motor and mental DA assessed by DASII at 1 year CA was 11.3±0.68 and 11.5±0.48 months. Motor and mental DA of extremely low birth weight infants were significantly lower (Table 2). Maternal education level and socio-economic status had no significant effect on motor and mental DA.

Table 1: Maternal and infant variables in relation to BG levels

Variables	Lowest BG below 10 <sup>th</sup> centile 51 mg% (n=60)	Lowest BG above 10 <sup>th</sup> centile >50 mg% (n=69)	p value
Gestational age in weeks* Mean (SD)	33.2 (2.7)	32.5 (2.4)	0.283
Birth weight in grams* Mean (SD)	1506.3 (338)	1482.4 (275)	0.66
Head circumference at birth in cm* Mean (SD)	29.3 (1.7)	29.5 (1.5)	0.61
Male <sup>†</sup> n (%)	32 (53)	36 (52)	0.895
Small for gestation <sup>†</sup> n (%)	18 (30)	13 (19)	0.14
Maternal age in years* Mean (SD)	26.7 (3.8)	26.4 (4.6)	0.65
Maternal PIH <sup>†</sup> n (%)	22 (36.6)	30 (43.5)	0.43
Apgar scores at 5 min <sup>‡</sup> Median (range)	8 (4-9)	9 (6-9)	0.22
Adequate AS in <34 weeks <sup>†</sup>	21 of 37 eligible	28 of 48 eligible	0.826
Normal delivery <sup>†</sup> n (%)	27 (45)	36 (52.2)	0.42
Extensive resuscitation <sup>§</sup> n (%)	3 (5)	1 (1.45)	0.39
Ventilation required <sup>†</sup> n (%)	28 (46.6)	31 (45)	0.84
Duration of ventilation (days)* Mean (SD)	5.1 (5.7)	5.1 (3.67)	0.16
Hypoxia <sup>§</sup> n (%)	1 (1.6)	4 (5.8)	0.23
Hypocarbica <sup>†</sup> n (%)	11 (18.3)	15 (21.7)	0.63
Hypercarbica <sup>§</sup> n (%)	4 (8.7)	6 (6.7)	0.67
Hyperoxia <sup>†</sup> n (%)	8 (13.3)	13 (18.8)	0.40
Peak bilirubin levels in mg%* Mean (SD)	11.4 (2.5)	11.5 (2.5)	0.89
Seizures <sup>§</sup> n (%)	1 (1.6)	1 (1.5)	0.92
Apnea <sup>†</sup> n (%)	11 (18.3)	13 (18.8)	0.94
Ductus treated <sup>†</sup> n (%)	15 (25)	20 (29)	0.74
Inotropes required <sup>†</sup> n (%)	8 (13.3)	6 (6.7)	0.40
Packed cell transfusion <sup>†</sup> n (%)	9 (15)	12 (17.3)	0.714
Culture positive sepsis <sup>§</sup> n (%)	2 (3.3)	2 (2.9)	0.89
IVH Grade I or II <sup>†</sup> n (%)	8 (13.3)	6 (6.7)	0.76
Parenteral nutrition <sup>†</sup> n (%)	17 (28.3)	18 (26)	0.74
Feed intolerance n (%)	14 (23.3)	9 (13)	0.13
Glucose levels ≤50 mg% after 72 h <sup>§</sup>	6 (10)	0	0.01

\*Student t-test, †Chi-square test, ‡Mann-Whitney test, §Fisher exact test. ventilation includes both CPAP and invasive ventilation, BG: Blood glucose, IVH: Intra-ventricular hemorrhage based on sonogram, AS: Antenatal steroids, CPAP: Continuous positive airway pressure, SD: Standard deviation

A significant difference in motor and mental DA at different levels of lowest BG was observed (Table 2). The lowest BG level of neonate had a significant positive correlation with their motor and mental DA assessed by DASII. The Pearson coefficient for motor and mental age was  $r=0.26$  ( $p=0.003$ ),  $r=0.2$  ( $p=0.035$ ), but for mean BG level, Pearson coefficient for motor and mental age was  $r=0.1$  ( $p=0.2$ ),  $r=0.08$  ( $p=0.36$ ), respectively.

The difference in mean motor and mental DA until a level of 50 mg% for lowest BG is significant, but at higher levels, there is no significant difference (Table 2). The mean motor DA by DASII at 1 year CA, when any BG <51 mg% ( $n=60$ ) and when all BG >50 mg% ( $n=69$ ) in first 72 h was  $11.1\pm 0.8$  and  $11.47\pm 0.6$  months, respectively. Similarly, mental DA by DASII in these groups was  $11.36\pm 0.52$  and  $11.59\pm 0.42$  months, respectively. Infants with symptomatic hypoglycemia had poor outcome compared to asymptomatic infants, but the number of episodes had no significant effect.

Poor composite outcome was seen in 12 infants and out of them, 8 (75%) had BG <51 mg%. Both motor and mental DQ <85% was seen in 11 infants and one had only mental DQ <85%.

Impaired hearing or vision and cerebral palsy were not seen in any infants. Birth weight and gestation-adjusted OR for poor composite outcome when lowest BG was below 10<sup>th</sup> centile (<51 mg%) was 2.83 (confidence interval [CI]=0.65-12.3) and adjusted OR for other variables is shown in Table 3.

## DISCUSSION

Ever since the landmark studies on neonatal hypoglycemia by Cornblath et al. [25], many studies have been done; however, the safe level above which there is no long-term or short-term risk is still not known [26]. Even the pediatric endocrine society recently recommended maintaining BG above 50 mg% in at risk infants until we get further evidence [27]. In this study also, we found a significantly lower DA at 1 year CA in infants when their lowest BG level was in lower range. But after adjusting for birth weight and gestation, there was no significant difference in the composite outcome. Several co-morbid factors as prematurity, birth weight, sepsis, shock, apnea, growth restriction, ventilation, social factors,

Table 2: Motor DA and mental DA by DASII assessment at 1 year corrected age

Variable	Motor DA by DASII in months Mean (SD)	p value	Mental DA by DASII in months Mean (SD)	p value
Gestational age*				
≤32 weeks (54)	11.25 (0.81)	0.37	11.42 (0.56)	0.24
>32 weeks (75)	11.36 (0.56)		11.52 (0.4)	
Birth weight†				
<1000 g (9)	10.1 (0.85)	0.02	10.6 (0.46)	0.04
1000-1499 g (54)	11.3 (0.65)		11.3 (0.65)	
1500-1999 g (66)	11.5 (0.5)		11.6 (0.4)	
Male (68)*	11.3 (0.7)	0.98	11.5 (0.5)	0.82
Female (61)	11.3 (0.65)		11.5 (0.5)	
SGA (31)*	11.1 (0.75)	0.08	11.37 (0.5)	0.12
AGA (98)	11.4 (0.64)		11.55 (0.45)	
Not ventilated‡ (70)	11.47 (0.47)	0.01	11.51 (0.42)	0.07
Ventilation <3 days (24)	11.31 (0.42)		11.33 (0.42)	
Ventilation >3 days (35)	10.9 (0.9)		11.32 (0.62)	
Socio-economic status‡				
Upper (25)	11.23 (0.85)	0.79	11.51 (0.58)	0.76
Middle (73)	11.34 (0.65)		11.45 (0.46)	
Lower (31)	11.33 (0.61)		11.52 (0.43)	
Lowest BG level†				
<30 mg% (14)	10.92 (0.83)	0.015	11.22 (0.62)	0.05
30-39 mg% (33)	11.12 (0.86)		11.35 (0.52)	
40-50 mg% (13)	11.43 (0.34)		11.37 (0.39)	
51-59 mg% (37)	11.54 (0.46)		11.49 (0.36)	
>60 mg% (32)	11.6 (0.36)		11.54 (0.42)	
Lowest BG level mg%*				
<51 (60) versus >50 (69)	11.06 (0.84), 11.46 (0.51)	0.001	11.34 (0.54), 11.56 (0.41)	0.004
<61 (97) versus >60 (32)	11.3 (0.7), 11.49 (0.63)	0.47	11.45 (0.47), 11.57 (0.48)	0.48
BG <51 mg% (60)*				
Symptomatic (13)	10.49 (1.03)	0.01	11.05 (0.57)	0.03
Asymptomatic (47)	11.35 (0.59)		11.46 (0.49)	
Episodes BG <51 mg% *				
<3 episodes (35)	11.14 (0.74)	0.62	11.48 (0.5)	0.26
≥3 episodes (25)	11.23 (0.68)		11.33 (0.45)	

\*Student t-test, †ANOVA test. DA: Developmental age, BG: Blood glucose, DASII: Developmental Assessment Scales for Indian Infants

Table 3: OR and unadjusted OR for composite outcome

Variable	n (%)		OR (95% CI)	aOR (95% CI)	P
	Poor composite outcome (n=12)	Good composite outcome (n=117)			
Lowest BG <51 mg%	8 (66.6)	52 (44.4)	2.3 (0.7-7.3)	2.83 (0.65-12.3)	0.18
Ventilation >3 days	8 (66.6)	27 (23.1)	6.6 (1.9-23.8)	3.12 (0.86-15.4)	0.08
SGA	6 (50)	25 (21.4)	3.6 (1.1-12.4)	2.7 (0.72-11.6)	0.35
Symptomatic and BG <51 mg%*	3 (37.5)	10 (15.2)	2.5 (0.5-12.3)	1.8 (0.3-14)	0.87
BG <51 mg% and ≥3 episodes*	4 (50)	21 (41.2)	1.5 (0.33-6.7)	1.2 (0.57-4.9)	0.74

\*Only for infants with BG <51 mg% (n=60, 8 infants had poor composite outcome). OR: Odds ratio, aOR: Adjusted odds ratio (adjusted for birth weight and gestational age), CI: Confidence interval, SGA: Small for gestation, BG: Blood glucose

hyperbilirubinemia, PDA, NEC, confound the outcome studies on neonatal hypoglycemia [28,29].

The outcome of neonatal hypoglycemia is quite conflicting, because of differences in inclusion criteria, study design, accuracy

of measured glucose, cut-off for hypoglycemia, age at follow-up duration, and timing of hypoglycemia [10]. Hypoglycemia in initial days of life is hypoketotic hypoglycemia with hyperinsulinism and preserved hepatic glycogen reserves in term and preterm infants [30]. Transitional hypoglycemia is considered a maturational process, but Kaiser et al. recently reported lower proficiency in language and mathematics at 10 years of age for infants who had only one BG <45 mg% at 3 h of age [31].

Brand et al. found no effect of transient hypoglycemia (plasma glucose <40 mg%) on outcome at 4 years, in large for gestation infants of non-diabetic mother by Denver scale and behavior checklist [8], but Haworth et al. reported a poor outcome at 3-4 years in infants of diabetic mother with hypoglycemia <20 mg% [9].

In this study, we found lower development outcome at 1 year CA when any BG was  $\leq 50$  mg% in first 72 h. In a similar high-risk group, Lucas et al. found a higher risk of developmental delay at 18 months CA, when plasma glucose was <47 mg% [27]. They also reported reduced mental score by 14 points (CI=22-6) and reduced motor score by 13 points (CI=20-5) if hypoglycemia occurred on 5 separate days [27]. In growth retarded infants, Duvanel et al. also reported delayed psychometric scores at 5 years when recurrent episodes of moderate hypoglycemia (BG <47 mg%) occurred [32]. The number of episodes of BG level  $\leq 50$  mg% had no significant effect on outcome in our study.

Duvanel et al. also reported a smaller head size at 5 years in infants who had neonatal hypoglycemia, which was not seen in our study [32]. There was a significant difference in DA at 1 year, between symptomatic and asymptomatic neonates with BG  $\leq 50$  mg% and the adjusted OR for poor composite outcome was 2.83 (0.65-12.3). Koivisto et al. and Singh et al. have reported poorer outcomes in symptomatic hypoglycemic infants [33,34]; but in our study, no neonate had hypoglycemic seizures and the outcomes of symptomatic and asymptomatic infants were similar. We found that BG level in the first 72 h of life did not influence the composite outcome at 1 year CA after adjusting for confounding variables. But Lucas et al., in a larger sample found that the number of episodes of hypoglycemia independently predicted the outcome at 18 months [27].

In our study, the mean BG in the first 2 h ( $52.2 \pm 19.7$  mg%) and levels in first 72 h are comparable to those reported by Srinivasan et al. and Heck and Erenberg in term infants [35,36]. The 5<sup>th</sup> and 10<sup>th</sup> centile (41 and 51 mg%) in the present study is higher than those reported in term infants [32,33], which may be due to early initiation of fluids or feeds based on the clinical condition. The incidence of hypoglycemia ( $\leq 50$  mg%) in this study was 46.5%. In similar high risk groups, the reported incidence by Lucas et al. and Duvanel et al. was 66% and 64% [27,32]. We found no difference in maternal and infant characteristics between infants with BG  $\leq 50$  mg% or  $> 50$  mg%. However, Lucas et al. found male sex, small for gestation, maternal preeclampsia, 5 min Apgar score <5, as risk factors for hypoglycemia in high-risk infants [27].

The merits of this study are the prospective data collection and accounting for various neonatal factors, which may influence the developmental outcome and their regular follow-up in

high-risk clinic. The limitations include 16% loss to follow-up, the main reason being residence far away (>100 km) and financial compensation for visits was not possible. Imaging studies could not be done due to logistic reasons. Follow-up studies from India and developing countries have reported dropout rates of 30-60% at 1-3 years [37,38]. We would definitely need a larger sample size and longer follow-up to identify academic or behavioral problems.

## CONCLUSION

We found a positive correlation of lowest BG level in high-risk neonates of birth weight <2000 g with their development outcome at 1 year CA. Although, high-risk infants with BG level  $\leq 50$  mg% are at added risk for delayed development at 1 year CA. Various other morbidities determine their outcome and larger studies are needed to make evidence-based recommendations on neonatal hypoglycemia.

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