RESEARCH PAPER

Screening for Hypoglycemia in Exclusively Breastfed High-risk Neonates

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Objective: To determine incidence of hypoglycemia in exclusively breastfed, high-risk but healthy newborns, and risk factors for its development. **Methods:** This observational study enrolled 407 exclusively breastfed high-risk (low birth weight newborns (1800-2499 g), late preterms, small-for-gestation, large-for-gestation and infant of diabetic mother), who did not require admission to neonatal intensive care unit and were kept in postnatal wards with mother. Hypoglycemia was defined as blood glucose ≤46 mg/dL (2.6 mmol/L). Blood glucose was monitored till 48 hours of life. **Results:** 27% of the screened newborns developed hypoglycemia in first 48 hours. 31 (7.6%) developed recurrent (>2) episodes, 28 (6.8%) had moderate (<37mg/dL) while 8 (1.9%) developed symptomatic hypoglycemia. With increase in birthweight, risk of hypoglycemia reduced significantly (*P*=0.003). Hypoglycemia was observed more frequently in first 2 hours as compared to next 48 hours (*P*=0.0001). Low birthweight, preterm gestation and male gender was significantly associated with increased risk of hypoglycemia. **Conclusion:** Healthy, high-risk exclusively breastfed newborns in postnatal wards need close monitoring for hypoglycemia in first 24 hrs of life.

Keywords: *Blood glucose, Feeding, Low birthweight, Management.*

Caregivers are often apprehensive whether newborns at risk for hypoglycemia, like small for gestational age (SGA), infants of diabetic mothers (IDM), large for gestation (LGA) and late-preterm infants, could be sustained on exclusive breastfeeding [1]. Hence they often offer supplemental feeding, especially in first 48-72 hrs, leading to low exclusive breastfeeding rates in the community [2-4]. These high-risk newborns are recommended to be screened for hypoglycemia, as it has been shown to be associated with poor neurological outcome [5]. Though incidence of hypoglycemia in high-risk neonates is well documented, its occurrence in exclusively breastfed high-risk newborns remains under-evaluated. Most studies on screening of hypoglycemia have been done on non-exclusive breastfed high-risk newborns or only LGA or SGA newborns, including those admitted in neonatal intensive care unit (NICU) [6-9]. We planned this study to document incidence of symptomatic and asymptomatic hypoglycemia in exclusively breastfed high-risk newborns. We also intended to evaluate risk factors for development of hypoglycemia in this population.

METHODS

This prospective cohort study was conducted at LLRM Medical College, Meerut, India between September 2011 to September 2012. We included all high-risk healthy newborns in postnatal ward whose mothers were willing for exclusive breastfeeding. High-risk group was defined as low birth weight (LBW) infants (1800-2500 g), late preterm (34-$36^{6/7}$weeks), SGA (birth weight <10^{th} percentile for gestational age), infants of diabetic mother (IDM) or LGA (birthweight >90^{th} percentile for gestational age). The birthweight percentiles were adopted from the National Neonatal and Perinatal Database (NNPD) growth charts [10]. Infants requiring NICU admission within first 48 hrs of life or those having major congenital malformations were excluded. The study was approved by institutional ethical committee of LLRM Medical College, Meerut, India. Informed written consent was obtained from parents. All the details of the newborn and mother were noted in a proforma at the time of enrolment.

Counseling as well as assistance for exclusive breastfeeding was done in all cases by nurses and doctors of Gynecology and Pediatrics department, as well as by distribution of pamphlets and display of posters. Breastfeeding was ensured within 30 minutes of birth in vaginal delivery and no later than 4 hrs of caesarean section, and thereafter every 2 to 3 hrs, including at least two nighttime feeds [11]. Blood glucose levels were monitored pre-prandial (preferred) at 1, 2, 6, 12, 24, and 48 hrs of life using glucometer strips (ACCU-CHEK Active, Serial no. GN 22012409, Germany) [12]. Duration, frequency of feeding, time since last feed, and if

any feed apart from breast milk was given, was documented. Confirmation of blood glucose by sending the sample to the laboratory was done only if the level was less than 25 mg/dL (1.1 mmol/L), if baby was symptomatic or if three consecutive readings of BGL remained ≤46 mg/dL. Hypoglycemia was defined as BGL ≤46 mg/dL (<2.6 mmol/L) [13]. For this study, moderate hypoglycemia was defined as BGL of 25 to <37 mg/dL (<2.1 mmol/L), while severe hypoglycemia as BGL <25 mg/dL (<1.38 mmol/L). Recurrent hypoglycemia was defined as 2 or more episodes of hypoglycemia in first 48 hrs of life.

Newborns developing asymptomatic hypoglycemia (25-46 mg/dL) were breastfed, and repeat blood glucose level was determined after 1 hr; if still in range of 25-46 mg/dL, baby was breastfed again and advised increased frequency of feeding, or increased volume if baby was given expressed breast milk (EBM) [13]. Supplementation with infant formula was done only if the level did not rise to >46 mg/dL despite breastfeeding/EBM >2 times. Monitoring was discontinued if the blood glucose level was >46 mg/dL on two consecutive measurements, and newborns were at least 48 hrs of age. Baby was admitted to the NICU and treated with intravenous dextrose as per standard protocols, if the level was <25 mg/dL or symptomatic hypoglycemia occurred at any time [14].

Data analyses were conducted using Stata 12.1 and P-value <0.05 was considered significant. A generalized estimating equations (GEE) model was used for comparison of blood sugar profile over 48 hours. Using logistic regression, Odd's ratio of incidence of hypoglycemia associated with each variable was calculated. Using the significantly associated variables with hypoglycemia, a multivariate logistic regression was built to identify the independent factors.

RESULTS

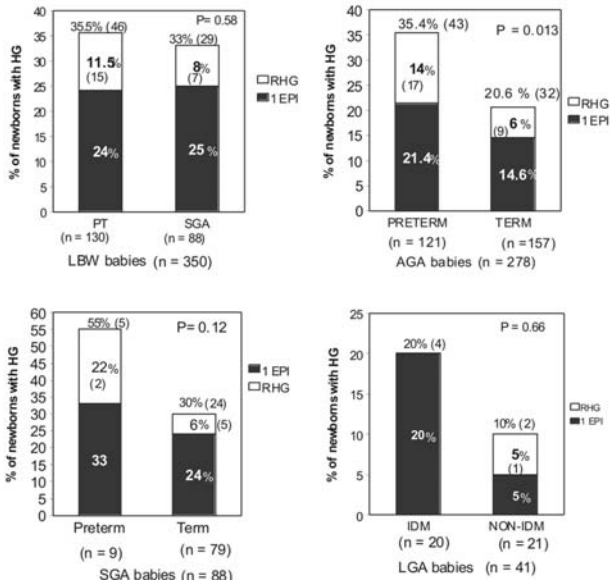
We enrolled 407 newborns, out of which 110 (27%) developed at least one episode of hypoglycemia in the first 48 hrs of life [95% CI 23-31%]. ***Table* I** and ***Fig.* 1** show incidence of hypoglycemia in different high risk groups and subgroups. Out of 110 neonates, 74 (67.2%) developed one episode of hypoglycemia, 36 (32.7%) newborns had recurrent episodes while 30 (27.2%), 5 (4.5%) and 1 (0.009%) newborn had two, three and four episodes of hypoglycemia, respectively (***Fig.* 1**). Applying a cut-off of blood glucose level of 40 mg/dL and 45 mg/dL, the incidence of hypoglycemia was 10.5% and 22.6%, respectively. Majority of newborns (92.7%) had asymptomatic hypoglycemia. Moderate hypoglycemia was observed in 28 (25.4%) newborns, of which 24 (21.8%) had hypoglycemia in first 6 hrs of life, but none of them had severe hypoglycemia. Among eight symptomatic newborns, 3 (37.5%) neonates developed jitteriness, 2 (25%) developed feeding intolerance, 2 (25%) developed lethargy and 1 (12.5%) had irritability. These eight newborns required intravenous fluids and were admitted to the NICU.

Incidence of hypoglycemia gradually decreased with time, from 44/407 (10.8%) at 1 hr to 1/298 (0.3%) at 48 hrs. Incidence of hypoglycemia was significantly more in first 2 hrs as compared to next 6 to 48 hrs (P=0.001). Mean (SD) blood glucose levels in both term and preterm neonates showed a significant gradual increase from 59.2 (15.9) mg/dL at 1 hr to 76.5 (14.5 mg/dL) at 48 hrs (P<0.01).

Out of 399 neonates, 17 (4.2%) received formula feeds as 5 (29.4%) neonates had persistent hypoglycemia and 4 (23.5%) mothers could not express enough breast milk. Despite euglycemia, 8 (40%) newborns were given

TABLE I CLINICAL CHARACTERISTICS OF HIGH-RISK NEONATES IN THE STUDY (N=407)

Characteristic	*Number (%)*	*Incidence (%)(95% CI)*	*OR(95% CI)*
Male gender	221 (54.3%)	32.1 (26.0, 38.7)	1.44 (1.12, 1.64)
Low birthweight	349 (85.7%)	29.5 (24.8, 34.6)	3.05 (1.34, 6.95)
Preterm delivery	130 (31.9%)	36.9 (28.6, 45.8)	2.03 (1.29, 3.20)
Large for gestation age	41 (10.1%)	14.6 (5.6, 29.2)	0.46 (0.19, 1.14)
Small for gestation age	89 (21.9%)	32.6 (23.0, 43.3)	1.30 (0.78 , 2.18)
Cesarian delivery	134 (32.9%)	30.6 (22.9, 39.1)	1.30 (0.82, 2.06)
Primigravide mother	151 (37.1%)	28.5 (21.4, 36.4)	1.12 (0.72, 1.76)
Illiterate mother	130 (32.1)	30.8 (23.0, 39.5)	1.33 (0.84, 2.11)
Diabetes mellitus	35 (9.6%)	28.6 (14.6, 46.3)	1.09 (0.50, 2.35)
Premature rupture of membranes	16 (4.0)	18.8 (4.0, 45.6)	0.61 (0.17, 2.19)
Hypertension during pregnancy	21 (5.2%)	33.3 (14.6, 57.0)	1.37 (0.54, 3.50)



HG= Hypoglycemia, LBW= Low birthweight, PT=Preterm, SGA=Small for gestation, LGA=Large for gestation, IDM=Infant of diabetic mother, AGA=Appropriate for gestation, RHG= Recurrent hypoglycemia, 1 EPI= Only 1 episode of hypoglycemia.

FIG. 1 *Incidence of hypoglycemia in different high risk group categories.*

formula milk by their family as their mothers could not successfully breastfeed despite counseling.

In first 6 hrs of life, preterm newborns had significantly lower blood glucose than term newborns but this difference was not significant beyond 6 hrs of life. Repeated measures regression analysis showed that at any point till 48 hrs, preterm newborns had about 4 mg/dL lower BGL than term newborns (95% CI; 1.48, 6.5 mg/dL; *P*=0.002). Hypoglycemic episodes were significantly more in preterm (36.9%) than term (22.4%) newborns (*P*=0.002). Odds of development of hypoglycemia in preterm infants was 2.02 times (95% CI 1.3, 3.2) that of term infants.

Hypoglycemic newborns were 170 g (95% CI 59, 280 g) lighter than those newborns who did not develop hypoglycemia within first 48 hrs of life (*P*=0.003). SGA and LGA newborns did not have higher incidence of hypoglycemia as compared to high-risk AGA newborns. Low birth weight (1.8 kg-2.5 kg), preterm gestation and male gender were independently significantly associated with the risk of hypoglycemia in exclusively breast fed newborns (by multivariate analysis) (***Table* I**). Pregnancy induced hypertension (PIH), premature rupture of membranes (PROM), diabetes mellitus with gestational diabetes (DM/GDM), mode of delivery, parity and educational status of mother were not found to have any significant association with blood glucose levels and risk of hypoglycemia (***Table* I**).

DISCUSSION

In this study, though incidence of hypoglycemia among high-risk exclusively breastfed newborns was 27%, there was no severe hypoglycemia, and very low incidence of symptomatic, moderate and recurrent hypoglycemia. Preterm gestation, low birth weight and male gender were significantly associated with hypoglycemia in this population.

We did not confirm hypoglycemia in each asymptomatic newborn by laboratory checks, as parents of asymptomatic, healthy, breastfeeding newborns often object to blood-letting and may resort to giving alternative milk for fear of more blood sampling. Also, we did not have a control group of non-high risk breastfed neonates, for it would have been unethical to screen them and give multiple pricks for blood sampling.

There is wide variation in the incidence of hypoglycemia reported in different groups of high-risk neonates [8,9,15] as well as in method of glucose estimation, cut-off of blood glucose level for defining hypoglycemia and population enrolled. Sasidharan, *et al*. [7] found similar incidence of hypoglycemia in SGA and preterm newborns in first 48 h of life [7], while others have reported lower incidence, albeit in different conditions [7,8,16]. Holtrop, *et al*. [8] had excluded newborns of diabetic mothers and their newborns were not exclusively breastfed [8]. Mejri, *et al*. [16] had included only term SGA infants, while Bhat, *et al*. [6] included all SGA newborns, whether breastfed, formula-fed, or on intravenous fluids. These factors could have lowered the incidence of hypoglycemia in their studies. As compared to our study, Harris, *et al*. [9] reported higher incidence of hypoglycemia in their population. Their incidence of moderate and recurrent hypoglycemia was also higher than that in our study [9].

Almost all our newborns with hypoglycemia were asymptomatic as reported in some other studies as well [9,10]. Bhat, *et al*. [6] have reported higher incidence of symptomatic hypoglycemia in SGA newborns. The only study on exclusively breastfed LBW neonates reported only 5% incidence of hypoglycemia using a similar/ different BGL cut-off [17]. However, as their study had smaller sample size, included only LBW neonates and did not describe the population characteristics in detail, results may not be comparable.

Current guidelines [18,19] of some forums recommend formula milk or dextrose infusion in asymptomatic hypoglycemia only after single

WHAT THIS STUDY ADDS?

- Neonates at high risk for hypoglycemia can be exclusively breastfed with close monitoring for at least 24 hours and management of asymptomatic hypoglycemia in these high-risk neonates is possible with repeated and frequent breastfeeding.

unsuccessful trial of feeding over 1 hr. On the contrary, our study point out that most of such high-risk babies can be managed by supervised repeated exclusive breastfeeding or EBM rather than top feeding. We conclude that healthy high-risk newborns in postnatal wards can be exclusively breastfed, but there is need to closely monitor their blood glucose levels at least in first 24 hrs, and asymptomatic hypoglycemia in newborns can be managed with frequent breastfeeds. More studies with long-term follow up are required to evaluate impact of this asymptomatic hypoglycemia on this population.

Contributors: AU: conceptualized and designed the study, monitored data collection and finalization of manuscript of the paper. PS: enrolled the subjects, collected and managed the data, and drafted the article; VS: analyzed and interpreted the data, reviewed the paper and provided important intellectual content; VJ: monitored the data collection and reviewed the draft paper. PS: reviewed the literature, and contributed in enrollment of subjects and data collection.
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