ORIGINAL RESEARCH

Patient profile, risk factors and short-term outcome of hypoglycemia in exclusively breastfed term neonates- experience of a tertiary care center

[1]Dr. Rajesh Kumar, [2]Dr. Girijanand Jha, [3]Dr. Vikash Chandra, [4]Dr. Nikki Kumari, [5]Dr. (Prof) Binod Kumar Singh, [6]Dr. Md Athar Ansari

[1]Assistant Professor, Department of Paediatrics, Nalanda Medical College and Hospital, Patna, Bihar, India.
[2]Senior Resident, Department of Paediatrics, Nalanda Medical College and Hospital, Patna, Bihar, India.
[3]Senior Resident, Department of Community Medicine, Indira Gandhi Institute of Medical Sciences, Patna, Bihar, India.
[4]Senior Resident, Department of Paediatrics, Nalanda Medical College and Hospital, Patna, Bihar, India.
[5]Professor and H.O.D, Department of Paediatrics, Nalanda Medical College and Hospital, Patna, Bihar, India.
[6]Associate Professor, Department of Paediatrics, Nalanda Medical College and Hospital, Patna, Bihar, India.

Corresponding Author
Dr. Girijanand Jha
Senior Resident, Department of Paediatrics, Nalanda Medical College and Hospital, Patna, Bihar, India

ABSTRACT
Background& Objectives: Hypoglycaemia is one of the commonest metabolic problems encountered in neonatal units. In most healthy neonates, these hypoglycaemic episodes are asymptomatic and do not adversely affect the short or long tern outcome. Occurrence of hypoglycemia in high-risk neonates is well studied and described in literature, but its occurrence in exclusively breastfed term newborns remains under-evaluated, more so in developing countries like ours. The present study was conducted to know the incidence, risk factors and short-term outcome of hypoglycemia in exclusively breastfed term neonates in a tertiary care level teaching institute.**Methods:**This hospital-based cohort study was conducted in postnatal ward of our hospital over two years from July 2019 to June 2021 including all term neonates whose mothers agreed for exclusive breastfeeding soon after birth. Relevant maternal and neonatal data regarding risk factors were recorded. Blood glucose levels (BGL) were preferably monitored before feedings at 2, 6, 12, 24, 48 and 72 hours of life using glucometer strips. Hypoglycemia was defined as BGL <45 mg/dL.**Result:**Over the 2-year study period we studied 831 neonates, out of which 209 or 25.1% had one or more episodes of hypoglycemia in the first 72 hours of their life. Mean birth weight of the neonates studied was 3.09 kg ± 0.47 Kg. Out of these 209 neonates, 144 (68.9%) had only one episode of hypoglycemia while the rest 65 (31.1%) had more than 1 episode of hypoglycemia. Majority of newborns (n=164, 78.5%) had asymptomatic hypoglycemia while 21.5% (n=45) had symptoms attributable to hypoglycemia. Incidence of hypoglycemia was significantly more in first 4 hrs as compared to next 6 to 48 hrs (P=0.01). Mean (SD) blood glucose level also showed a significant gradual increase from 58.53±14.9 mg/dL at 6 hours to 89.6± 15.4mg/dl at 48 hrs (P<0.01). In univariate analysis, low birth weight (<2.5 kg), SGA, LGA, primigravida mother, LSCS delivery, unbooked case and maternal BMI >30 Kg/m2 were significantly associated with occurrence of hypoglycemia.**Conclusion:**A significant proportion of exclusively breastfed high-risk term newborns do suffer from hypoglycemia. Though such neonates can be effectively managed in postnatal ward, their blood glucose levels need to be monitored at least for the first 72 hours of life with special emphasis on the first 4 hours.
Key words: Blood glucose, incidence, hypoglycemia, breastfed, term.

INTRODUCTION

Hypoglycaemia is one of the commonest metabolic problems encountered in neonatal units. In most healthy neonates, these hypoglycaemic episodes are asymptomatic and do not adversely affect the short or long tern outcome. They perhaps only reflect normal processes of metabolic adaptation to extrauterine life. However, when hypoglycaemic episodes are prolonged or recurrent, they may manifest with acute systemic effects and adverse neurologic outcome.[1] Beyond 20 weeks of gestation, normal lower limit of concentration for foetal glucose is around 54 mg/dl.[2]

During intrauterine phase, the foetus is completely dependent on mother for glucose, amino acids, free fatty acids, ketones, and glycerol supplies, to be used for its own energy needs.[3] After birth, these newborns have to adapt from having a continuous source of glucose from the mother during intrauterine life to maintaining its own supply of glucose, both during periods of fasting and in between feedings.[4] Newborns' blood glucose concentration is about 70% of the maternal level, at the time of birth and decreases further to reach its nadir by about 1 hour of life to blood sugar level of around 20-25 mg/dl.[5] However, this nadir is transient and blood glucose level begins to rise again. The maintenance of normal glucose levels in newborns depends upon adequate glycogen stores, maturation of glycogenolytic and gluconeogenic pathways and an adequate integrated endocrine response.[6] This postnatal adaptation is responsible for maintaining glucose homeostasis in a newborn. Few newborns, especially those with certain risk factors like small for gestational age, preterm neonates and infants of diabetic mothers, fail to make this adaptation and are thus having altered glucose homeostasis and low plasma glucose levels.[7] The operational threshold for hypoglycaemia is defined as "that concentration of plasma or whole blood glucose at which clinicians should consider intervention, based on the evidence currently available in literature".[8,9] This operational threshold for hypoglycaemia is currently believed to be a blood glucose value of <40mg/dl (plasma glucose <45mg/dl), in both term and preterm babies. WHO defines neonatal hypoglycemia as blood glucose level of <45 mg/dl.

It is prudent to state that preventive measures, early recognition and prompt treatment of hypoglycemia are extremely important in high-risk neonates to minimize any adverse outcomes associated with hypoglycaemic episodes. Guardians are generally apprehensive if their neonates who are at risk for hypoglycemia (like small for gestational age or SGA, infants of diabetic mothers or IDM, large for gestation or LGA and late-preterm infants), could be sustained on exclusive breastfeeding. Hence, they have a tendency to offer supplemental feeding, especially in first 48-72 hrs of life presuming inadequate milk production by mother's breasts. This leads to low exclusive breastfeeding rates in the community and is associated with hazards of bottle feeding/unhygienic feeding practices. These high-risk newborns are recommended to be screened for hypoglycemia, as hypoglycaemic events have been shown to be associated with poor neurological outcome.[10] Though occurrence of hypoglycemia in high-risk neonates is well studied and described in literature, its occurrence in exclusively breastfed term newborns remains under-evaluated, more so in developing countries like ours. Infact, 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. Based on this background, the present study was conducted at our tertiary care level teaching institute to study occurrence of symptomatic and asymptomatic hypoglycemia in such neonates.

AIM AND OBJECTIVES
- To study the incidence of hypoglycaemic episodes in exclusively breastfed term neonates.
- To study associated risk factors like sex, gestational age, birth weight, maternal age, maternal BMI, Maternal morbidity like diabetes mellitus, hypertension, mode of delivery, parity etc
- To study the time of onset of hypoglycemia and short-term outcome of such children.

MATERIALS AND METHODS
Study duration: two years fromJuly 2019 to June 2021
Study setting: Postnatal ward at Nalanda Medical College and Hospital. Patna, Bihar, India.
Study design: hospital-based cohort study.
Inclusion and exclusion criteria: All term neonates born during the aforementioned period were assessed for eligibility in this study. All such neonates in the ward whose mothers agreed for exclusive breastfeeding soon after birth were offered to participate in this study. Infants requiring NICU admission within first 48 hrs of life or those having major congenital malformations were excluded from this study. Information so obtained was compiled in a structured proforma. Maternal data regarding age, parity antenatal care, presence of risk factors e.g., eclampsia, pregnancy induced hypertension, diabetes mellitus etc. were noted in a structured proforma. All neonates were weighed at birth with an electronic weighing machine with an accuracy of ±5gm. The birth weight percentiles were adopted from the Fenton growth charts. Gestational age assessment was done by the Modified New Ballard Score. Counselling as well as assistance for exclusive breastfeeding was done in all cases by nurses and doctors of Gynaecology and Paediatrics 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 2 hrs of caesarean section, and thereafter every 2 to 3 hrs, including at least two nighttime feeds. Blood glucose levels were preferably monitored before feedings at 2, 6, 12, 24 48 and 72 hours of life using glucometer strips (Dr Morepen Glucometer). Duration, frequency of feeding, time since last feed, and if any feed apart from breast milk was given, was documented. Confirmation of blood glucose level (BGL) by sending the sample to the laboratory was done only if the level was less than 30 mg/dl or if the hypoglycaemic episode was symptomatic. Hypoglycemia was defined as BGL <45 mg/dL. 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 72 hrs of life. Newborns developing asymptomatic hypoglycemia with blood glucose >25 mg/dl were immediately 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. 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.

STATISTICAL ANALYSIS

Information so collected was tabulated and entered in Microsoft excel sheet and further analysed by SPSS ver.20® software for Windows. Variables were expressed as mean, standard deviation, percentages, proportions or percentiles as appropriate. We used Pearson's chi-square test for categorical parameters and independent samples' t test for continuous parameters. P-value <0.05 was taken as significant.

RESULT

Over the 2-year study period we studied 831 neonates, out of which 209 or 25.1% had one or more episodes of hypoglycemia in the first 48 hours of their life. Mean birth weight of the neonates studied was 3.09 kg ± 0.47 Kg. Out of these 209 neonates, 144 (68.9%) had only one episode of hypoglycemia while the rest 65 (31.1%) had more than 1 episode of hypoglycemia (2 episodes in 29, 3 episodes in 22, 3 episodes in 10 and 4 episodes in 4 neonates). Majority of the newborns (n=164, 78.5%) had asymptomatic hypoglycemia while 21.5%(n=45) had symptoms attributable to hypoglycemia. Among these symptomatic newborns, 18 (37.8%) neonates had jitteriness, 14 (31.1%) were lethargic, 7 (15.5%) had seizures, 4 (8.9%) had feeding intolerance, and 2 (4.4%) had irritability. These 45 newborns required intravenous fluids and were admitted to the NICU. Table 1 depicts general characteristics of the study population.

Table 1: General characteristics of the neonates with hypoglycemia

Characteristics	Number	Percentage
Male Gender	119	56.9%
Low birth weight	97	46.4%
Small for gestational age	86	41.1%
Large for gestational age	24	11.5%
Born by LSCS	124	59.3%
Primigravida mother	139	66.5%
Infant of diabetic mother	22	10.5%
Premature rupture of membranes	18	8.6%
Pregnancy induced hypertension	12	5.7%

Incidence of hypoglycemia gradually decreased with time, from 91/831 (10.9%) to 64/831 (7.7%) at 12 hours to 41/831 (4.9%) at 24 hours, 10/831 (1.2%) at 48 hours and 3/831 (0.4%) at 72 hours of age. Incidence of hypoglycemia was significantly more in first 4 hrs as compared to next 6 to 48 hrs (P=0.01). Mean (SD) blood glucose level also showed a significant gradual increase from 58.53±14.9 mg/dL at 6 hours to 89.6± 15.4mg/dl at 48 hrs (P<0.01). Out of these 831 neonates, 38 (4.6%) subsequently received formula feeds. 21 of these could not express enough breast milk and so were advised to give formula milk but 7 (33.3%) of such neonates suffered from hypoglycaemia. Despite euglycemia, 17 (44.7%) newborns were given formula milk by their family as their mothers could not successfully breastfeed despite counselling. Hypoglycaemic newborns were 178 g (95% CI 62, 274 g) lighter than those newborns who did not develop hypoglycemia within first 48 hrs of life (P=0.002). SGA and LGA newborns had higher incidence of hypoglycemia as compared to AGA newborns (p<0.001). In univariate analysis, low birth weight (<2.5 kg), primigravida mother, LSCS delivery, unbooked case and maternal BMI >30 Kg/m2 were significantly associated with occurrence of hypoglycemia in such neonates. On the other hand, male gender, pregnancy induced hypertension (PIH), premature rupture of membranes (PROM) and socioeconomic status of mother were not found to have any significant association with blood glucose levels and risk of hypoglycemia.

Table 2. Clinical characteristics and occurrence of hypoglycemia in the study population

Characteristics		Number (%) (N=831)	Incidence of hypoglycemia	% of hypoglycaemic events (N= 209)
Sex	Male	454(54.6%)	119 (14.3%)	56.93%
	Female	379(45.6%)	90 (10.8%)	43.06%

Birth weight	<2.5 kg	236(28.4%)	97 (11.7%)	46.4%
	2.5-3.8 kg	526(63.3%	90 (10.8%)	43.1%
	>3.8 kg	69 (8.3%)	22 (10.5%)	10.5%
Status at birth	AGA	541(65.1%)	99 (11.9%)	47.36%
	SGA	218(26.2%)	86(10.3%)	41.14%
	LGA	72 (8.7%)	24 (2.9%)	11.48%
Maternal age	<30 years	481(57.9%)	126(15.2%)	60.3%
	>30 years	350(42.1%)	83(10.0%)	39.7%
Maternal BMI (Kg/sq m)	18.5-25	426(51.3%)	134(16.1%)	64.1%
	25-30	327(39.3%)	48 (5.8%)	22.9%
	>30	78 (9.4%)	27 (3.2%)	12.9%
Mode of delivery	Vaginal	561(67.5%)	85 (10.2%)	40.7%
	LSCS	270(32.5%)	124 (14.9%)	59.3%
Parity	Primigravida	236(28.4%)	139(16.7%)	66.5%
	Multigravida	595(71.6%)	70 (8.4%)	33.5%
Antenatal care	Booked case	719(86.5%)	173(20.8%)	82.8%
	Unbooked case	112(13.5%)	36 (4.3%)	17.2%
Residence	Rural	508(61.1%)	77 (9.3%)	36.8%
	Urban	323(38.9%)	132(15.9%)	63.2%
Socioeconomic class	Lower	531(63.9%)	142(17.1%)	67.9%
	Middle	294(35.4%)	66(7.9%)	31.6%
	Upper	6 (0.7%)	1 (0.1%)	0.5%
Maternal comorbidity	DM	54(6.5%)	22 (2.6%)	10.5%
	PIH	85(10.2%)	12 (1.5%)	5.7%
	DM + PIH	17(2.1%)	4 (0.5%)	1.9%
Rupture of membranes	Premature	204(24.5%)	18 (2.1%)	8.6%
	Mature	627(75.5%)	19123.0%)	91.4%

DISCUSSION

The present study intended to study the occurrence of hypoglycemia in exclusively breastfed term neonates, who are most often thought to be free from any metabolic complications. In the present study 25.1% of such neonates suffered from hypoglycemia within 72 hours of their life. Singh et al[11] in their Indian study have reported slightly higher incidence (27%) of hypoglycemia, but they had also included late preterm infants in their study. The wide variation in incidence of hypoglycemia reported can be attributed to method of glucose estimation, cut-off of blood glucose level for defining hypoglycemia and population enrolled. Holtrop et al.[12] had excluded newborns of diabetic mothers and their newborns were not exclusively breastfed. Mejri et al.[13] had included only term SGA infants, while Bhat et al.[14] included all SGA newborns, whether breastfed, formula-fed, or on intravenous fluids. These factors could have altered the incidence of hypoglycemia in their studies. As compared to our study, Harris et al.[7] reported higher incidence of hypoglycemia in their population. Majority of the newborns with hypoglycemia were asymptomatic in the present study which is comparable to the findings of National Neonatal Perinatal Database Human Reproduction Research Centre Network.[15] A study on exclusively breastfed LBW neonates reported only 5% incidence of hypoglycemia using a similar/different BGL cut-off.[16] However, their study had smaller sample size,

included only LBW neonates and did not describe the population characteristics in detail.

The incidence of hypoglycemia was higher in males as compared to females, but this difference was not statistically significant. The incidence of hypoglycemia was significantly higher in low-birth-weight babies. This is also suggested by the Indian study of Saini et al.[17] Similarly, we also found a higher incidence of hypoglycemia in SGA and LGA neonates as compared to AGA neonates. This could be attributed to abnormalities in postnatal adaptation to glucose homeostasis is these neonates. Incidence of hypoglycemia was higher in mothers <30 years of age. This is similar to the finding of Kumar TJ et al.[18] where they found that incidence of hypoglycemia in infants born to mothers less than 30 years of age was 38%, while the incidence in infants born to ≥ 30 years was 18.9%. There was no statistically significant difference in occurrence of hypoglycemia in neonates born to mothers with PIH or PROM. Most cases of hypoglycemia occurred on first day of life and that too mostly within the first 4 hours of life. Bhat et al.[14] on their study on SGA babies reported that almost all the episodes of hypoglycemia occurred within 24 hours. In the present study, hypoglycemia was seen upto 3rd day of life suggesting a need for frequent monitoring of blood glucose values till 72 hours with special attention to the 1st 4 hours of age.

Some forums recommend formula milk or dextrose infusion in asymptomatic hypoglycemia only after single unsuccessful trial of feeding over 1 hr.[19] On the

contrary, we found that most of such high-risk neonates can be managed by supervised repeated exclusive breastfeeding or EBM rather than top feeding. We believe that healthy high-risk newborns in postnatal wards can still be managed by exclusively breastfeeding, but there is need to closely monitor their blood glucose levels at least in the 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 asymptomatic hypoglycemia on this population.

CONCLUSION
A significant proportion of exclusively breastfed high-risk term newborns do suffer from hypoglycemia. LBW, SGA, LGA, IDM and unbooked cases are more likely to suffer from hypoglycemia. Though such neonates can be effectively managed in postnatal ward, their blood glucose levels need to be monitored at least for the first 72 hours of life with special emphasis on the first 4 hours. Asymptomatic hypoglycemia in newborns needs to be detected and managed promptly.

LIMITATIONS
First limitation is that we did not have a control group of non-high risk breastfed neonates. Though it could have added more weight to our study, it would have been unethical to screen them and give multiple pricks for blood sampling. Second limitation is that we did not confirm hypoglycemia in each asymptomatic newborn from a venous blood sample. We actually feared that parents of asymptomatic, healthy, breastfeeding newborns would object to blood-letting and resort to giving alternative milk for fear of more blood sampling. Third limitation is that ours was a single centre study with moderate sample size. There's need for larger multi-centric studies on this issue for making general recommendations.

FINANCIAL DISCLOSURE
We declare that our study has not received financial support of any kind.

CONFLICT OF INTEREST
None to declare.

REFERENCES
1. Termote B, Verswijvel G, Gelin G, Palmers Y. Neonatal hypoglycemic brain injury. JBR-BTR. 2008; 91:116-7.
2. Thompson-Branch A, Havranek T. Neonatal Hypoglycemia. Pediatr Rev. 2017 Apr; 38(4):147-57.
3. Kalhan SC, D'Angelo L, Savin SM, Adam PAJ. Glucose production in pregnant women at term gestation: Sources of glucose for human fetus. J Clin Invest. 1979; 63:388-94.
4. Heck LJ, Erenberg A. Serum glucose levels in term neonates during the first 48 h of life. J Pediatr. 1987; 110:119-22.
5. Srinivasan G, Pildes RS, Cattamanchi G, Voora S, Lilien LD. Plasma glucose values in normal neonates: a new look. J Pediatr. 1986; 109:114-7.
6. Committee on Fetus and Newborn. Adamkin DH. Postnatal glucose homeostasis in late-preterm and term infants. Pediatrics. 2011 Mar;127(3):575-79
7. Harris DL, Weston PJ, Harding JE. Incidence of neonatal hypoglycemia in babies identified as at risk. J Pediatr. 2012; 161: 787-91.
8. Tin W. Defining neonatal hypoglycaemia: a continuing debate. Semin Fetal Neonatal Med. 2014 Feb;19(1):27-32
9. Cornblath M, Hawdon JM, Williams AF, Aynsley-green A, Ward-platt MP, et al. Controversies regarding definition of neonatal hypoglycemia: Suggested operational thresholds. Pediatrics. 2000; 105: 1141-45.
10. Shah R, Harding J, Brown J, McKinlay C. Neonatal Glycaemia and Neurodevelopmental Outcomes: A Systematic Review and Meta-Analysis. Neonatology. 2019;115(2):116-126.
11. Singh P, Upadhyay A, Sreenivas V, Jaiswal V, Saxena P. Screening for hypoglycemia in exclusively breastfed high-risk neonates. Indian Pediatr. 2017; 54(6): 477–80.
12. Holtrop PC. The frequency of hypoglycaemia in full-term large and small for gestational age newborns. Am J Perinatol. 1993;10:150-4.
13. Mejri A,Dorval VG, Nuyt AM, Carceller A. Hypoglycaemia in term newborns with a birth weight below the 10th percentile. Paediatr Child Health.2010;15:271-5.
14. Bhat MA, Kumar P, Bhansali A, Majumdar S, Narang A. Hypoglycaemia in small for gestational age neonates. Indian J Pediatr. 2000;67:423-27.
15. Report 2002-2003: National Neonatal Perinatal Database Human Reproduction Research Centre Network. New Delhi: National Neonatology Forum of India; 2006. (National Neonatal Perinatal Database Human Reproduction Research Centre Network).
16. Murty VY, Ram KD. Study of pattern of blood sugar levels in low birth weight neonates who are exclusively on breast milk. Journal of Dr. NTR University of Health Scinces. 2012;1:90-93.
17. Saini A, Gaur BK, Singh P. Hypoglycemia in low birth weight neonates: Frequency, pattern, and likely determinants.IJCP.2018;5: 526-32
18. Kumar TJ, Vaideeswaran M, Seeralar AT. Int J Contemp Pediatr. 2018 Sep;5(5):1952-55.
19. Narayan S, Wazir S, Mishra S. Management of Neonatal Hypoglycaemia. NNF Clinical Practice Guidelines 2011; Available at: http://www.nnfi.org/images/pdf/nnf_cpg_consolidated_file-january102011.pdf.(Last accessed April 1,2023)