Neonatal hypoglycemia revisited: Incidence and clinical profile in a tertiary center hospital of Tripura

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ABSTRACT

Introduction: Hypoglycemia is a common but preventable metabolic abnormality in neonates associated with long-term sequelae. Controversies still exist about its definition, screening methodology, management, and outcome making it a subject for further exploration. **Objectives:** The study was taken up to find out the proportion of neonate developing hypoglycemia in the neonatal intensive care unit (NICU) and to study the clinical profile of hypoglycemia in neonates. **Materials and Methods:** All intramural and extramural neonates admitted in the NICU within 2 h of delivery were included in this study. They were screened for hypoglycemia using Accutrend-alpha glucometer. Results along with all neonatal and maternal variables were recorded and analyzed using the SPSS version 15.0. **Results:** The current study shows the prevalence of hypoglycemia as 32.2%. Proportion of hypoglycemia was more in small for gestational age, large for gestational age neonates, and neonates with prematurity, birth asphyxia, and maternal diabetes mellitus. Besides, hypoglycemia occurred more commonly within 24 h of life. Lethargy, convulsion, apnea, and jitteriness were common presenting symptom. **Conclusion:** The present study shows despite advances in obstetrical practices and increase in institutional deliveries over years, neonatal hypoglycemia continues to occur with almost same frequency along with the same maternal and neonatal variables.

Key words: *Large for gestational age, Neonatal hypoglycemia, Premature rupture of membrane, Small for gestational age*

Hypoglycemia is the most common but preventable metabolic abnormality in neonates. Prolong neonatal hypoglycemia may result in irreversible brain damage, mental retardation, recurrent seizure activity, personality disorders, and even death. The pathological changes are characterized by atrophic gyri, reduced myelination, and atrophy of cerebral white matter [1]. Blood glucose is essential for normal neurological function and development. Poor reserve of liver glycogen and fat and immature metabolic pathway at birth predisposes preterm and small for gestational age (SGA) neonates to prolonged hypoglycemia[1-3]. In perinatal asphyxia, high fuel requirement of anaerobic metabolism, the depletion of stores, and a delay in metabolic adaptation are possible underlying mechanisms of hypoglycemia. Neonatal hyperinsulinism and hypoglycemia occur in infants of diabetic mothers (IDMs). Other known causes of neonatal hypoglycemia are islet cell dysregulation syndrome (nesidioblastosis), Beckwith–Wiedemann syndrome, insulin-secreting adenoma, congenital hypopituitarism, glycogen storage diseases, defects of amino acids metabolism, defects of gluconeogenesis, and defects of β-oxidation of fatty acids [4-6].

The definition of hypoglycemia in the newborn has remained controversial due to lack of significant correlation between plasma glucose concentration, clinical symptoms, and its long-term sequelae [7]. Hypoglycemia is defined as a glucose concentration two standard deviations below the mean of a particular population. In healthy term neonates, serum glucose values are rarely <35 mg/dl between 1 and 3 h of life, <40 mg/dl from 3 to 24 h, and <45 mg/dl after 24 h [8,9]. The incidence of hypoglycemia varies with definition, population, method, and timing of feeding and the type of glucose assay. The overall incidents vary from 1 to 5/1000 live birth, but it has been estimated to occur in up to 16% of large for gestational age (LGA) neonates and 15% of SGA neonates and 5–10% in preterm neonates [8,10].

Neonatal hypoglycemia is a subject to be reexplored as the relation between plasma glucose concentration, clinical symptoms, and its long-term sequelae is poorly understood, controversies exist over its best way of detection, despite increase in institutional deliveries and advances in neonatal care practices neonatal hypoglycemia continues to occur. This study was taken up to find out the proportion of neonates developing hypoglycemia in the neonatal intensive care unit (NICU) and to study the clinical profile of hypoglycemia in neonates.

MATERIALS AND METHODS

This hospital-based cross-sectional study was conducted in the NICU, Department of Pediatrics in a tertiary care teaching hospital of Agartala over a period from November 2015 to August 2017.

Neonates admitted within 2 h of life in inborn and outborn NICU during the study period consisted of the study population. The sample size was determined using the following formula suitable for cross-sectional clinical studies[11], $N=Z^2 P (1–P)/d^2$; where, N = minimum sample score; Z = Standard normal deviate value corresponding to 95% confidence interval (=1.96); P = Estimated prevalence (29% prevalence was used [12]), d = degree of precision (set=5%). Therefore, $N=1.96^2 \times 0.29 (1–0.29)/0.0025 = 316$. Questionnaires, patient profile records, and investigation reports were the study tools. The study was carried out after approval from the institutional ethical committee. Written informed consent from the parents was taken before recruiting the neonate into the study.

All term and preterm neonates admitted in inborn and outborn NICU within 2 h of delivery during the study period were included in the study. Neonates, with gross congenital malformations which are life threatening or have the potential to result in disability and neonates whose parents did not consent for inclusion in the study, were excluded from the study. All term and preterm neonates admitted in inborn and outborn NICU within 2 h of delivery during the study period were screened for hypoglycemia after getting informed consent from the parents/guardians.

After thorough hand wash, pre-warmed sole was pricked with a sterile lancet. A drop of blood was collected to the curved edge of the test strip to completely cover the yellow color on the strip. Test result was read within 30 sec. For the study purpose, operational threshold for hypoglycemia was defined as random blood sugar <40 mg/dl for both initial 48 h and beyond [13]. Blood sugar was screened just before feeding by Accutrend-alpha glucometer at 2, 6, 12, 24, 48, and 72 h of age and/or whenever symptoms suggestive of hypoglycemia developed. For critically sick neonate such as those with perinatal asphyxia, sepsis, and shock, blood sugar was screened every 6 h in active phase of the illness.

Accutrend-alpha glucometer worked on the principle of bio-amperometry and had a sensitivity of 98% and specificity of 93% for detecting neonatal hypoglycemia (<40 mg/dl) with a positive predictive value of 88% and negative predictive value of 99% [14,15]. For babies who showed blood sugar level <40 ml/dl, a second blood sample was sent to laboratory immediately for estimation of whole blood sugar levels and hypoglycemia managed according to the standard treatment protocol [16]. A detailed history for all cases was taken with emphasis on the antenatal, natal, and postnatal events. Thorough clinical examination including general physical examination and systemic examination was done. In addition, required samples were also sent for relevant investigations from diagnosis and management point of view depending on the case.

In asymptomatic babies, oral feeds were given and blood sugar tested after 30 min, if repeat blood sugar was >40 mg/dl, 2 hourly feeding was given with 6 hourly monitoring of blood sugar for 48 h. If repeat blood sugar value was still <40 mg/dl, I.V. glucose infusion at 6 mg/kg/min was started. In symptomatic babies, an intravenous (IV) bolus of 2 ml/kg of 10% dextrose was given followed by glucose infusion at 6 mg/kg/min. Blood sugar checked after 30 min. If the blood sugar value still was <40 mg/dl, glucose infusion was increased at 2 mg/kg/min and blood sugar rechecked after 30 min. Once blood sugar level was maintained >40 mg/dl and then blood sugar level was checked at 2 h. After 24 h of IV glucose therapy, once two consecutive blood sugar levels were >40 mg/dl, the infusion was tapered off at 2 mg/kg/min every 6 h with blood sugar level monitoring. Tapering was accompanied by concomitant increase in oral feeds. Once a rate of 4 mg/kg/min of glucose infusion was achieved and oral feeding was adequate and the blood sugar level was consistently >40 mg/dl, the infusion was stopped. In cases of refractory hypoglycemia (hypoglycemia persisting beyond 7 days of life despite glucose infusion rates of 12 mg/kg/min for >24), hydrocortisone, diazoxide, octreotide, and glucagon were used [16].

Data were recorded, compiled, and analyzed with computer using the SPSS version 15.0. Raw data were grouped as per neonatal risk factors such as gestational age, birth weight, and as per intrauterine growth curve, and maternal risk factors such as maternal diabetes mellitus, eclampsia, premature rupture of membrane (PROM), antenatal steroid, chorioamnionitis, mode of delivery, and maternal fever. Statistical tests such as χ^2 test and Fisher's exact test were used as per applicability. $p<0.05$ was considered as statistically significant.

RESULTS

In the present study, of 320 neonates admitted in NICU, 103 (32.2%) neonates developed at least one episode of hypoglycemia during the hospital stay. Of 320 newborn enrolled in the study, 168 (58.1%) were male and 134 (41.9%) were female. Out of these, 35% of the male neonates and 27.6% of the female neonates had hypoglycemia. Majority (64%) of the hypoglycemic episodes occurred within 24 h of life. Another 28% of the hypoglycemic episode occurred between 24 and 72 h of life. Only 8% of the hypoglycemic episode occurred beyond 72 h of life.

A total of 61.5% of preterm babies (gestational age <37 weeks) and 15.3% of term neonates developed hypoglycemia ($p<0.0001$). The incidence of hypoglycemia is also significantly higher in neonates with birth weight <2.5 kg (56.7%) or >4 kg (73.6%) than in neonates with normal birth weight ($p=0.0000$). Furthermore, hypoglycemia was significantly more among SGA (45%) and LGA (63.2%) babies in comparison to appropriate for gestational age (AGA) babies ($p=0.0000$). Besides, the incidence of hypoglycemia was more in asphyxiated babies (48.3%) than in non-asphyxiated babies (22.5%) ($p<0.0001$) as shown in Table 1.

Significantly higher incidence of hypoglycemia was found in IDMs (66.7%) than in neonates born to non-diabetic mothers (26.1%) ($p=0.000$). However, no significant difference was found with respect to the presence or absence of maternal fever, PROM, eclampsia, maternal IV fluids, antenatal corticosteroid, history of chorioamnionitis, and mode of delivery (Table 2). In the present study, 11% of cases of the documented hypoglycemia were asymptomatic. Among the symptomatic cases, the leading symptoms found were lethargy (45.63%), convulsion (20.38%),

Table 1: Distribution of NH in relation to neonatal variables

Parameters	Hypoglycemia (%)	No hypoglycemia (%)	p value
Gestational age (weeks)			
≥37	31 (15.3)	172 (84.7)	<0.0001
<37	72 (61.5)	45 (38.5)	
Birth weight (kg)			
<2.5	55 (56.7)	42 (43.3)	<0.0001
2.5–4	34 (16.7)	170 (83.3)	
>4	14 (73.6)	5 (26.3)	
Gestational age			
SGA	50 (45)	61 (55)	<0.0001
AGA	41 (21.5)	149 (78.4)	
LGA	12 (63.2)	7 (36.8)	
Birth asphyxia			
Present	58 (48.3)	62 (51.7)	<0.0001
Absent	45 (22.5)	155 (77.5)	

SGA: Small for gestational age, AGA: Appropriate for gestational age, LGA: Large for gestational age. NH: Neonatal hyperbilirubinemia

Table 2: Distribution of NH in relation to maternal variables

Maternal variables	Hypoglycemia (%)	No hypoglycemia (%)	p value
Diabetes mellitus			
Present	32 (66.7)	16 (33.3)	<0.0001
Absent	71 (26.1)	201 (73.9)	
Eclampsia			
Present	7 (53.8)	6 (46.2)	0.1263
Absent	96 (31.3)	211 (68.7)	
PROM			
Present	9 (45)	11 (55)	0.2217
Absent	94 (31.3)	206 (68.7)	
Antenatal steroid			
Present	30 (25.6)	87 (74.4)	0.0630
Absent	73 (36)	130 (64)	
Chorioamnionitis			
Present	2 (22.2)	7 (77.8)	0.7256
Absent	101 (32.5)	210 (67.5)	
Mode of delivery			
Vaginal	42 (27.8)	109 (72.2)	0.1207
LSCS	61 (36)	108 (64)	
Maternal fever			
Present	8 (53.3)	7 (46.7)	0.0902
Absent	95 (31.1)	210 (68.8)	
Received IV fluids			
Present	33 (25.8)	95 (74.2)	0.0510
Absent	70 (36.5)	122 (63.5)	

PROM: Premature rupture of membrane, LSCS: Lower segment cesarean section. NH: Neonatal hyperbilirubinemia, IV: Intravenous

apnea (9.71%), jitteriness (7.76%), and hypothermia (5.82%) in descending order of frequency.

DISCUSSION

In this study, the incidence of neonatal hypoglycemia was 32.2% among the neonates admitted in NICU. Osier *et al*. [17], in 2003, from Kenya, Sasidharan *et al*. [18], in 2004, from Kerala, India, Lodhi *et al*. [12], in 2006, from India, Dashti *et al.* [19], in 2007, from Tehran, De *et al*. [20], in 2011, from Kolkata, India, and Singh *et al.* [21], in 2014, from Manipur, India, reported the prevalence of neonatal hypoglycemia as 23%, 4.1%, 29.1%, 15.1%, 32.6%, and 15.2%, respectively. Our finding is similar to that of Lodhi *et al*. [12] and De *et al*. [20]

In our study, 64% of the hypoglycemic episodes occurred within 24 h of life. Bhat *et al*. [22], in 2000, Sasidharan *et al*. [18], in 2005, and Ayoub *et al*. [8], in 2013 reported that 98%, 65.6%, and 62.5% neonates develop hypoglycemia during the 1st day of life, respectively. Our observation is close to that of Sasidharan *et al*. [18] and Ayoub *et al.* [8].We also observed that neonatal hypoglycemia between 24 and 72 h of life developed in 28% of cases and beyond 72 h, in 8% of babies. Ayoub *et al.* [8] reported that 31.1% of the neonates developed hypoglycemia between 24 and 72 h of life and 6.2% after 72 h of life. Our observation is in close proximity to that of Ayoub *et al*. [8].

Hypoglycemia was found among 58.1% of male and 41.9% of female neonates in this series. Singh *et al.* [21] also found male predominance of hypoglycemia (16.99% in male vs. 13.33% in female). Similar results have also been reported by Hamid and Chishti from Pakistan [23]. Hypoglycemia was more common in preterm newborns (61.5%) than in newborns with gestational age >37 weeks (15.3%) in the present study. Singh *et al.* [21] reported hypoglycemia in 19.05% of preterm and 14.42% of term neonates. Burdan *et al.* [24] reported hypoglycemia in 52.8% preterm and 45.53% term neonates. De *et al.* [20] found that 77.77% of preterm and 22.95% of term neonates had hypoglycemia. All these studies demonstrated a preponderance of hypoglycemia in preterm neonates.

In the present series, hypoglycemia was more commonly seen in newborns with birth weight <2.5 kg and >4 kg than in normal birth weight babies (p=0.000). Similarly, De *et al*. [20] found higher incidence of hypoglycemia in low birth weight (LBW) babies than in normal birth weight babies (64% vs. 14%, respectively). Bhand *et al*. [25] also found that 26% LBW babies had hypoglycemia. In this study, hypoglycemia was more in SGA and LGA neonates than in AGA neonates (p=0.00). Ho *et al.* [26] from Malaysia reported a higher incidence of hypoglycemia in SGA (34.2%) than in AGA neonates (16.6%). Burdan *et al.* [24] also reported more hypoglycemia (45.16%) in SGA than in AGA neonates (33.66%). Similar observations were also made by Dhananjaya and Kiran [27] and De *et al.* [20] in their studies.

In the present study, a higher incidence of hypoglycemia was observed in IDMs (p<0.001). Similar results were found in the studies conducted by Dhananjaya and Kiran [27] and Sasidharan *et al.* [18] and they also reported significantly higher incidence of hypoglycemia in neonates born to diabetic mother. On the contrary, Bhand *et al*. [25] observed lower incidence of hypoglycemia (13%) in neonates born to diabetic mother. This difference might be due to difference in the study design.

Other maternal factors including maternal fever, PROM, eclampsia, IV fluids, antenatal corticosteroid, chorioamnionitis, and mode of delivery did not show a significant difference in the incidence of hypoglycemia in their neonates. Similarly, Ayoub *et al.* [8] found that maternal hypertension was not a risk factor for hypoglycemia. On the contrary, Sasidharan *et al*. [18] reported a higher incidence of hypoglycemia in babies (50%) of mother with eclampsia. This difference might be due to difference in sample size. Pettit *et al.* [28] reported a higher rate of hypoglycemia in neonates exposed to antenatal steroid (5.7% vs. 4.2%). This difference might be due to the difference in sample size and study design.

In this study, a higher incidence of hypoglycemia was observed in neonates with birth asphyxia ($p<0.0001$). Other studies have shown a variable incidence of hypoglycemia in birth asphyxia ranging from 57.1% in a study done by Sasidharan *et al*. [18] to as low as 15% in a study done by Babu *et al.* [29]. Moreover, as many as, 11% of cases of the documented hypoglycemia were asymptomatic in the present study. Among the symptomatic cases, the leading symptoms found were lethargy (45.63%) and convulsion (20.38%). Singhal *et al*. [30] observed lethargy (81.4%), jitteriness (67.4%), respiratory abnormality (41.9%), hypotonia (39.5%), seizure (30.2%), and cyanosis (18.6%) in decreasing order of frequency**.** Many other studies have shown similar observations.

CONCLUSION

The present study showed the incidence of hypoglycemia as 32.2% among the neonates admitted in NICU. The proportion of hypoglycemia was more in neonates with prematurity, birth asphyxia, maternal diabetes mellitus, and in LGA and SGA neonates. It was also observed that hypoglycemia occurred more commonly within 24 h of life. Lethargy, convulsion, apnea, and jitteriness were the common presenting symptom.

REFERENCES

1. Sperling MA. Hypoglycemia. In: Kliegman RM, Behrman RE, Jensen HB, Stanton BF, editors. Nelson Textbook of Pediatrics. 19th ed. Philadelphia, PA: Elsevier Inc.; 2012. p. 517-31.
2. Cornblath M, Schwartz R, Aynsley-Green A, Lloyd JK. Hypoglycemia in infancy: The need for a rational definition. A ciba foundation discussion meeting. Pediatrics 1990;85:834-7.
3. Ghai OP. Ghai Essential Pediatrics: New Born Infants. 8th ed. New Delhi: CBS Publication; 2013. p. 179-80.
4. Anysley GA, Soltesza G. Disorders of blood glucose homeostasis in the neonate. In: Robertson NR, editors. Textbook of Neonatology. London: Churchill Livingstone; 1986. p. 605-21.
5. Landon MB, Gabbe SG, Piana R, Mennuti MT, Main EK. Neonatal morbidity in pregnancy complicated by diabetes mellitus: Predictive value of maternal glycemic profiles. Am J Obstet Gynecol 1987;156:1089-95.
6. Saudubray JM, Narcy C, Lyonnet L, Bonnefont JP, Poll The BT, Munnich A, *et al*. Clinical approach to inherited metabolic disorders in neonates. Biol Neonate 1990;58 Suppl 1:44-53.
7. Kalhan S, Peter-Wohl S. Hypoglycemia: What is it for the neonate? Am J Prenatal 2000;17:11-4.
8. Ayoub NI, Hanoudi BM, Naif MH. Evaluation of maternal and neonatal risk factors for neonatal hypoglycemia. Iraqi J Community Med 2013;1:13-8.
9. Thompson-Branch A, Havranek T. Neonatal hypoglycemia. Pediatr Rev 2017;38:147-57.
10. Jain A, Aggarwal R, Sankar MJ, Agarwal R, Deorari AK, Paul VK. Hypoglycemia in the newborn. Indian J Pediatr 2010;77:1137-42.
11. Ogundipe L. Sample size determination in clinical research: 1. Hosp Med 2000;61:730-2.
12. Lodhi MA, Shah NA, Shabir G. Risk factors associated with neonatal hypoglycemia. Prof Med J 2006;16:687-90.
13. Hay WW Jr., Raju TN, Higgins RD, Kalhan SC, Devaskar SU. Knowledge gaps and research needs for understanding and treating neonatal hypoglycemia: Workshop report from Eunice Kennedy shriver national institute of child health and human development. J Pediatr 2009;155:612-7.
14. Makaya T, Memmott A, Bustani P. Point-of-care glucose monitoring on the neonatal unit. J Paediatr Child Health 2012;48:342-6.
15. Griffiths AD, Bryant GM. Assessment of effects of NH: A study of 41 cases with matched controls. Arch Dis Childhood 1971;46:819-27.
16. Agarwal R, Deorari AK, Paul VK. Clinical Protocols 2014-WHO Newborn CC. New Delhi: CBS Publishers; Hypoglycemia. Available from: http://www.newbornwhocc.org/clinical_proto.html. [Last cited on 2015 Dec 20].
17. Osier FH, Berkley JA, Ross A, Sanderson F, Mohammed S, Newton CR, *et al*. Abnormal blood glucose concentrations on admission to a rural Kenyan district hospital: Prevalence and outcome. Arch Dis Child 2003;88:621-5.
18. Sasidharan CK, Gokul E, Sabitha S. Incidence and risk factors for neonatal hypoglycaemia in Kerala, India. Ceylon Med J 2004;49:110-3.
19. Dashti N, Einollahi N, Abbasi S. Neonatal hypoglycemia: Prevalence and clinical manifestations in Tehran children's hospital. Pak J Med Sci 2007;23:340-3.
20. De AK, Samantha M, Kundu CK. Study of blood glucose levels in normal and low birth weight neonates and impact of early breast feeding in a tertiary care centre. Ann Niger Med 2011;51:53-8.
21. Singh YP, Devi TR, Gangte D, Devi TI, Singh NN, Singh MA. Hypoglycemia in newborn in Manipur, India. J Med Soc 2014;28:108-11.
22. Bhat MA, Kumar P, Bhansali A, Majumdar S, Narang A. Hypoglycemia in small for gestational age babies. Indian J Pediatr 2000;67:423-7.
23. Hamid H, Chishti AL. Neonatal hypoglycemia. An underreported entity in high-risk neonates. Pak Pediatr J 2000;24:9-11.
24. Burdan DR, Botiu V, Teodorescu D. Neonatal hypoglycemia. The incidence of the risk factors in savator VUIA obstetrics-gynecology hospital, ARAD. Timisoara Med J 2009;59:77-80.
25. Bhand SA, Sheikh F, Siyal AR, Nizamani MA, Saeed M. Neonatal hypoglycemia. Presenting pattern and risk factors of neonatal hypoglycemia. Prof Med J 2014;21:745-9.
26. Ho J, Malaysian Very Low Birth Weight Study Group. Mortality and morbidity of the small for gestational age (SGA) very low birth weight (VLBW) Malaysian infant. Singapore Med J 2001;42:355-9.
27. Dhananjaya CD, Kiran B. Clinical profile of hypoglycemia in newborn babies in rural hospital setting. Int J Biol Med Res 2011;2:1110-4.
28. Pettit KE, Tran SH, Lee E, Caughey AB. The association of antenatal corticosteroids with neonatal hypoglycemia and hyperbilirubinemia. J Matern Fetal Neonatal Med 2014;27:683-6.
29. Babu RM, D'Souza JL, Susheela C. Study of incidence, clinical profile and risk factors of neonatal hypoglycemia in a tertiary care hospital. Int J Pediatr Res 2016;3:753-7.
30. Singhal PK, Singh M, Paul VK, Deorari AK, Ghorpade MG, Malhotra A, *et al*. Neonatal hypoglycemia--clinical profile and glucose requirements. Indian Pediatr 1992;29:167-71.

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