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Neonatal Hypoglycemia

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Study of Incidence, Risk Factors and Clinical Profile of Neonatal Hypoglycemia in a Tertiary Care Hospital

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Background: The clinical manifestations of hypoglycemia are non-specific. Studying the incidence, and identifying clinical features and risk factors associated with hypoglycemia, may help in preventing neurological damage. **Materials and Methods:** This prospective observational study was done over 6 months in GMC Mahasamund. All babies admitted to NICU with whole blood sugar levels <40 mg/dl were subjected to detailed history, thorough clinical examination and observation of signs and symptoms. **Results:** Neonatal hypoglycemia constituted about 11.7% of the neonates among which 56% were preterm,56% were outborn and 44% were inborn. A greater number of male babies (67%) had hypoglycemia with a male-to-female ratio of 2:1. Asymptomatic hypoglycemia was noticed in 56% and symptomatic in 44%. The major clinical manifestations were jitteriness(57.9%) followed by lethargy(42.1%), convulsions(26.3%) and apnoeic spells(15.8%). We noticed PIH as the most significant maternal risk factor accounting for (37.2%) followed by APH(16.4%). Chronic diabetes mellitus and gestational diabetes were both associated with 4.7% of cases. We found prematurity the most associated neonatal risk factor accounting for 55.8% of cases. Birth asphyxia and IUGR accounted for 21.1% of cases each among inborn babies. Early onset sepsis was found in 41.7% and birth asphyxia in 33.3% among outborn babies. Persistent hypoglycemia was noted in 6.9% of cases. **Conclusion:** Neonatal hypoglycemia constituted 11.7% of NICU admissions. Proper monitoring of blood glucose levels should be done to plan early treatment and prevent neurological damage.

Keywords: Hypoglycemia, Blood Sugar Levels, Neurological Damage

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Introduction

The term hypoglycemia refers to a reduction in the glucose concentration of circulating blood. It is recognised that 23-50% of infants admitted to NICU are diagnosed with one or more episodes of hypoglycemia [1]. Being a tertiary care centre, we receive a lot of referrals from nearby hospitals and many times proper health facilities like adequate warmth, oxygen supply and medical staff accompaniment are not provided to babies during transport leading to increased morbidity and mortality, so a comparative study was done between inborn and outborn babies.

The clinical manifestations of hypoglycemia are nonspecific and similar to those of many disorders in newborn infants [2]. Most cases of neonatal hypoglycemia are transient, respond readily to treatment and are associated with an excellent prognosis [3]. Persistent hypoglycemia is more likely to be associated with abnormal endocrine conditions and possible neurological sequelae [4]. Studying the incidence may help to plan the services, and identifying the clinical features and risk factors associated with neonatal hypoglycemia may help in preventing neurological damage [5].

In the majority of healthy neonates, the frequently observed low blood glucose concentrations are not related to any significant problem and merely reflect normal processes of metabolic adaptation to extrauterine life. However, when low blood glucose levels are prolonged or recurrent, they may result in acute systemic effects and neurologic sequelae [6]. The fetus in utero is entirely dependent on the mother for glucose. At the time of birth, the neonate must abruptly switch from having a continuous supply of glucose from the maternal blood in fetal life to maintaining its supply of glucose during periods of fasting, and when feedings are interspersed intermittently [7]. Postnatal hypoglycemia in newborn infants remains an important clinical problem and prolonged periods of hypoglycemia may be associated with poor neurodevelopmental outcomes. Since prolonged periods of low plasma glucose are associated with an increased risk of neurodevelopmental impairment, it is an important priority to prevent hypoglycemia in newborn infants [8]. Certain risk groups, including small for gestational age infants, preterm infants, and infants of diabetic Mothers, are at high risk of hypoglycaemia [9]. Prevention, early diagnosis, and prompt treatment are important for high-risk infants who develop hypoglycemia, to minimize the severity and duration of hypoglycaemic episodes, which are associated with adverse outcomes [10]. This study aimed to find out the incidence of hypoglycemia in exclusively breastfed, high-risk newborns, and to study associated risk factors like gender, gestational age, birth weight, and time of onset of the development of hypoglycemia.

Materials and Methods

Study design: Cross-sectional observational hospital-based study

Study duration: January 2022 to June 2022

Study setting: This study was conducted in the NICU of GMC Mahasamund.

Study population: A total of 367 neonates admitted to NICU during the study period were studied

Inclusion criteria: All neonates admitted to NICU during the study period.

Exclusion criteria:

- Babies with congenital malformations.
- Babies with inborn errors of metabolism
- Maternal glucose infusion

Methodology/ Data Collection: All babies admitted to NICU were subjected to random glucose estimation by strip method using a glucometer and in babies who showed blood sugar levels <40 mg/dl, serum samples were sent to the lab immediately for estimation of whole blood sugar level by oxidase method using autoanalyser.

Babies with whole blood sugar values <40 mg/dl in both the samples were taken up for the study and sugar values were repeated after 2,4,8,12,24 and 48 hours. These babies were subjected to detailed history taking, thorough clinical examination and investigations.

Statistical analysis

1. All relevant data were entered into pre-designed proforma and analysed (with the help of a statistician) using Microsoft SPSS software for Windows Version 20.0 and Microsoft Excel 2010.

2. Data were expressed as a percentage and mean +/- SD.

3. The chi-square test was used to analyse the significance of the difference between the distribution of data.

4. P-value <0.05 was considered as statistically significant.

Results

Neonatal hypoglycemia constituted about 11.7% of the neonates among which 56% were preterm,56% were outborn and 44% were inborn.

A greater number of male babies (67%) had hypoglycemia with a male-to-female ratio of 2:1. Asymptomatic hypoglycemia was noticed in 56% and symptomatic in 44%. The major clinical manifestations were jitteriness(57.9%) followed by lethargy(42.1%), convulsions(26.3%) and apnoeic spells(15.8%). We noticed PIH as the most significant maternal risk factor accounting for (37.2%) followed by APH(16.4%). Chronic diabetes mellitus and gestational diabetes were both associated with 4.7% of cases. We found prematurity the most associated neonatal risk factor accounting for 55.8% of cases. Birth asphyxia and IUGR accounted for 21.1% of cases each among inborn babies. Early onset sepsis was found in 41.7% and birth asphyxia in 33.3% among outborn babies. Persistent hypoglycemia was noted in 6.9% of cases.

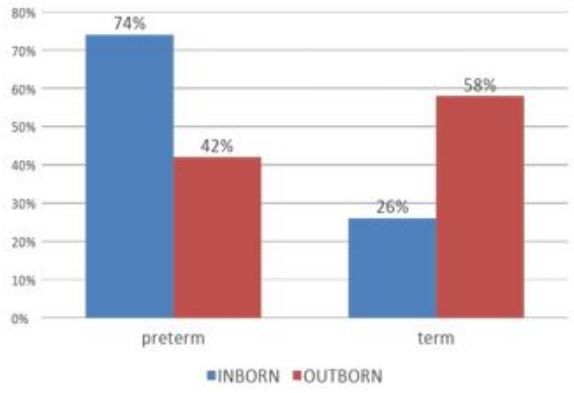

Figure 1: Distribution of neonates based on gestational age and type of birth.

Among inborn babies, 74% were preterm and 26% were term. Among outborn babies, 42% were preterm and 58% were term.

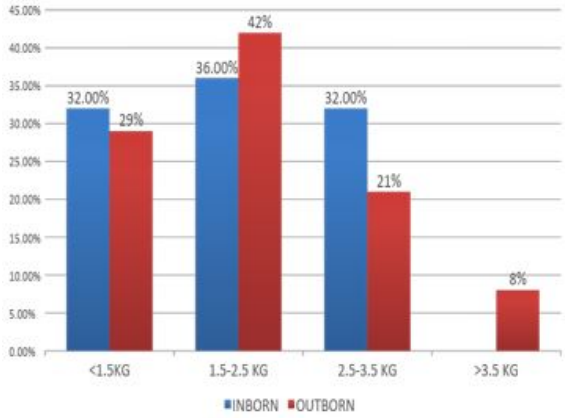

Figure 2: Distribution of neonates based on birth weight.

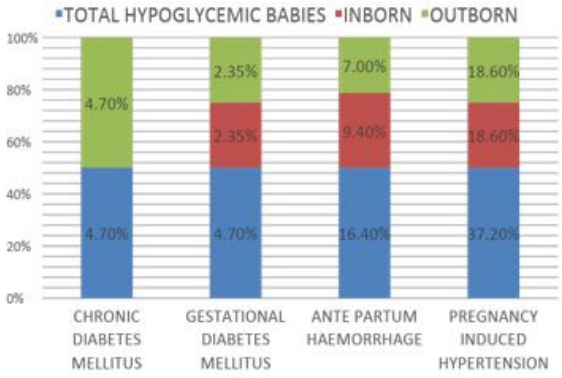

Figure 3: Maternal risk factors associated with hypoglycemia.

The most common maternal risk factor associated with hypoglycemia was found to be PIH(37.2%) followed by APH (16.4%).

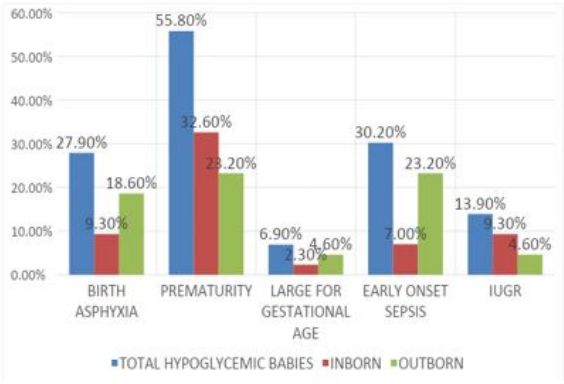

Figure 4: Neonatal risk factors associated with hypoglycemia.

The most common neonatal risk factor was found to be prematurity (55.8%), followed by early onset sepsis (30.2%) and birth asphyxia (27.9%).

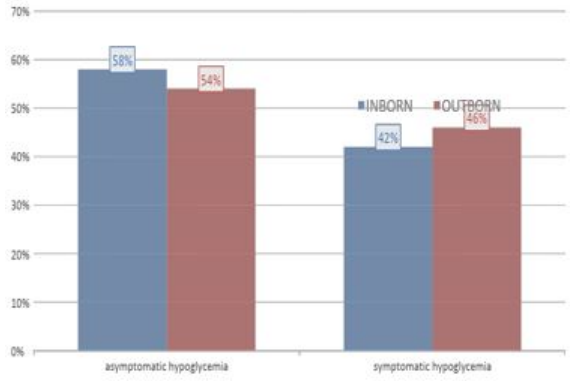

Figure 5: Types of hypoglycemia noted.

Among inborn, 58% had asymptomatic hypoglycemia and 42% were symptomatic. 54% of outborn babies had asymptomatic hypoglycemia and 46% were symptomatic.

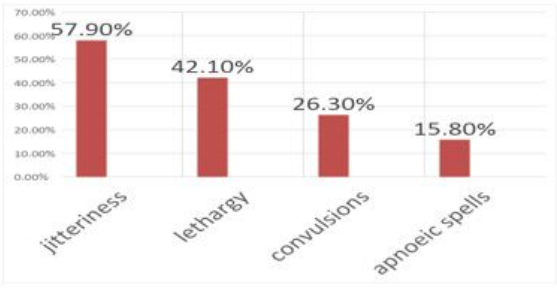

Figure 6: Clinical symptoms noted in symptomatic hypoglycemia.

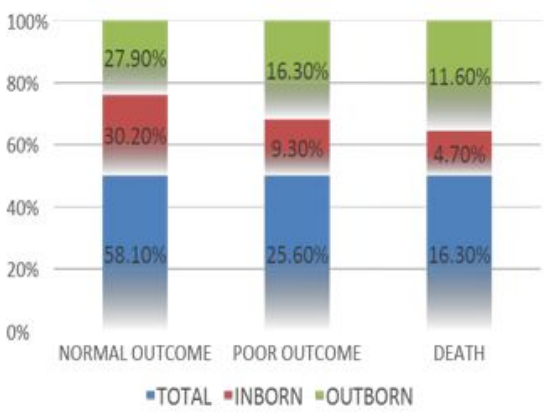

Figure 7: Outcome of hypoglycemia noted among inborn and outborn neonates.

Out of the total hypoglycemic babies, 58.1% had normal outcomes, 25.6% had poor outcomes and 16.3% died.

Table 1: Risk of hypoglycaemia associated with different maternal and neonatal factors – Univariate analysis for Inborn babies.

Characteristics	Level	Hypoglycemia/ Total	OR [95% CI]	P-value
MATERNAL				
History of DM (Mother)	No	19 /143 (13.3%)	Ref	
	Yes	0/7 (0%)	-	
Gestational Diabetes	No	18/146 (12.3%)	Ref	0.465
	Yes	1/4 (25%)	2.37 (0.23 - 24.03)	
Gestational age (weeks)	<=27	1/4 (25%)	2.4 (0.28 - 25.4)	0.467
	28-31	1/20 (5%)	0.38 (0.05 - 3.15)	0.369
	32-35	4/44 (15.9%)	1.36 (0.48 - 3.87)	0.562
	36-39	10/82 (12.2%)	Ref	
APH	No	15/133 (11.3%)	Ref	0.163
	Yes	4/17 (23.5%)	2.42 (0.69 - 8.39)	
PIH	No	11/133 (8.3%)	Ref	< 0.0001
	Yes	8/17 (47.1%)	9.86 (3.17 - 30.6)	
Type of delivery	NVD	12/69 (17.4%)	Ref	0.115
	LSCS	7/81 (8.6%)	0.45 (0.17 - 1.21)	
NEONATAL				
Sex	Female	7/62 (11.3%)	Ref	0.671
	Male	12/88 (13.6%)	1.24 (0.46 - 3.35)	
Birth weight (gms)	< 1000	1/10 (10%)	0.82 (0.09 - 7.62)	0.857
	1001 - 1499	5/27 (18.5%)	1.67 (0.46 - 6.07)	0.439
	1500 - 2499	7/63 (11.1%)	0.92 (0.28 - 2.92)	0.883
	> 2500	6/50 (12.0%)	Ref	
Hypothermia	No	19/145 (13.1%)	Ref	
	Yes	0	-	
Birth asphyxia	No	15/103 (14.6%)	Ref	0.307
	Yes	4/47 (8.5%)	0.55 (0.17 - 1.74)	
Prematurity	No	5/66 (7.6%)	Ref	0.105
	Yes	14/84 (16.7%)	2.44 (0.83 - 7.16)	
Small for gestational age	No	15/134 (11.2%)	Ref	0.128
	Yes	4/16 (25%)	2.64 (0.76 - 9.25)	
Large for gestational age	No	18/145 (12.4%)	Ref	0.621
	Yes	1/5 (20%)	1.76 (0.18 - 16.7)	
Sepsis	No	16/131 (12.2%)	Ref	0.662
	Yes	3/19 (15.8%)	1.35 (0.35 - 5.14)	

The univariate analysis showed only PIH as the influencing factor of hypoglycaemia. In the INBORN category, the risk of hypoglycaemia was 9.86 (95% CI: 3.17 – 30.6) times higher in PIH mothers as compared to those without PG.

Although other factors like gestational diabetes, APH, LSCS, Birth asphyxia, Prematurity and SGA showed risk of hypoglycaemia, but the odds were statistically insignificant.

Since only single factor indicated significance, multivariate analysis was not performed.

Table 2: Risk of hypoglycaemia associated with different maternal and neonatal factors – Univariate analysis for Outborn babies.

Characteristics	Level	Hypoglycemia/ Total	OR [95% CI]	P-value
MATERNAL				
History of DM (Mother)	No	22/214 (10.3%)	Ref	0.022
	Yes	2/3 (66.6%)	17.45 (1.52 - 200.4)	
Gestational Diabetes	No	23/209 (11.0%)	Ref	0.895
	Yes	1/8 (12.5%)	1.15 (0.14 - 9.81)	
Gestational age (weeks)	<=27	2/6 (33.3%)	4.9 (0.82 - 29.9)	0.041
	28-31	6/49 (12.2%)	1.38 (0.49 - 3.92)	0.369
	32-35	4/31 (12.9%)	1.47 (0.44 - 4.91)	0.532
	36-39	12/131 (9.2%)	Ref	
APH	No	21/205 (10.2%)	Ref	0.129
	Yes	3/12 (25.0%)	2.92 (0.73 - 11.64)	
PIH	No	16/200 (8.0%)	Ref	< 0.0001
	Yes	8/17 (47.1%)	10.22 (3.47 - 30.12)	
Type of delivery	NVD	22/187 (11.8%)	Ref	0.415
	LSCS	2/30 (6.7%)	0.54 (0.12 - 2.41)	
NEONATAL				
Sex	Female	7/74 (9.5%)	Ref	0.589
	Male	17/143 (11.9%)	1.29 (0.51 - 3.27)	
Birth weight (gms)	< 1000	4/20 (20.0%)	2.75 (0.72 - 10.52)	0.139
	1001 - 1499	3/37 (8.1%)	0.97 (0.24 - 3.98)	0.967
	1500 - 2499	10/76 (13.2%)	1.67 (0.60 - 4.62)	0.326
	> 2500	7/84 (8.3%)	Ref	
Hypothermia	No	23/195 (11.8%)	Ref	0.324
	Yes	1/22 (4.5%)	0.36 (0.05 - 2.77)	
Birth asphyxia	No	16/125 (12.8%)	Ref	0.344
	Yes	8/92 (8.7%)	0.65 (0.26 - 1.59)	
Prematurity	No	14/127 (11.0%)	Ref	0.984
	Yes	10/90 (11.1%)	1.00 (0.43 - 2.38)	
Small for gestational age	No	22/198 (11.1%)	Ref	0.938
	Yes	2/19 (10.5%)	0.94 (0.20 - 4.35)	
Large for gestational age	No	22/210 (10.5%)	Ref	0.156
	Yes	2/7 (28.6%)	3.42 (0.63 - 18.7)	
Sepsis	No	14/185 (7.6%)	Ref	< 0.0001
	Yes	10/32 (31.2%)	5.55 (2.20 - 14.0)	
Inadequate transport	No	3/45 (6.7%)	Ref	0.299
	Yes	21/172 (12.2%)	1.95 (0.55 – 6.84)	

In the Outborn category, the risk of hypoglycaemia was 17.45 (95% CI: 1.52 – 200.6) times higher in mothers with a history of DM as compared to those without a history (p=0.022). The risk of hypoglycaemia was 4.9 (95% CI: 0.82 – 29.9) times higher in mothers with gestational age <= 27 weeks as compared to those with normal gestation (p=0.047). Further, the risk was 10.22 (95% CI:3.47 – 30.12) times higher in PIH cases as compared to non-PIH cases (p < 0.0001). Sepsis had an increased risk of hypoglycaemia with OR of 5.55 (95% CI: 2.20 – 14.0) with p < 0.00

Table 3: Risk of hypoglycaemia associated with different maternal and neonatal factors – Multivariate analysis for Outborn babies.

Characteristics	Level	Hypoglycemia/ Total	OR [95% CI]	P-value
MATERNAL				
History of DM (Mother)	No	22/214 (10.3%)	Ref	0.022
	Yes	2/3 (66.6%)	34.59 (2.28 – 523.78)	
Gestational age (weeks)	<=27	2/6 (33.3%)	4.91 (0.51 - 46.89)	0.168
	28-31	6/49 (12.2%)	1.18 (0.33 - 4.28)	0.797
	32-35	4/31 (12.9%)	1.55 (0.36 - 6.56)	0.553
	36-39	12/131 (9.2%)	Ref	
PIH	No	16/200 (8.0%)	Ref	< 0.0001
	Yes	8/17 (47.1%)	14.82 (4.02 - 54.66)	
NEONATAL				
Sepsis	No	14/185 (7.6%)	Ref	< 0.0001
	Yes	10/32 (31.2%)	9.22 (3.03 - 28.25)	

In the Outborn category, the factors significant in univariate analysis were considered together in multivariate logistic regression analysis, with the results shown in Table 3. The history of DM had a significant risk associated with hypoglycaemia with OR of 34.59 (95% CI: 2.28 – 523.78) and p-value

0.022. Further, PIH had an associated OR of 14.82 (95% CI: 4.02 – 54.66) with a p-value < 0.0001. Also, the presence of sepsis increased the risk of hypoglycaemia by 9.22 (95% CI: 3.03 – 28.25) times with a p-value < 0.0001.

Discussion

Neonatal hypoglycemia is a common metabolic problem due to the inability of the body to maintain glucose homeostasis. The overall prevalence depends on the definition of hypoglycemia, criteria for diagnosis of hypoglycemia, diagnostic methods and other factors. Hence there is a wide range of differences in the incidence of hypoglycemia ranging from 4 to 15 %. Hypoglycemia can be symptomatic or asymptomatic. Undiagnosed hypoglycemia can have long-term neurological consequences; thus the emphasis is on prevention and early detection along with treatment of hypoglycemia. The reported incidence of hypoglycemia varies a lot due to controversies regarding the definition of neonatal hypoglycemia and the criteria for diagnosis of hypoglycemia. A study from Iran has taken blood sugar levels less than 50 mg/dl as criteria for diagnosis of hypoglycemia [11]. Similar to some recent Chinese and Indian studies [12,13]. we have taken blood sugar levels less than 40 mg/dl as criteria for diagnosis of hypoglycemia [Table 3].

Table 4: Comparison of incidence of hypoglycemia with other studies.

Study	No. of babies admitted to NICU	No. of babies with hypoglycemia	Incidence
Present Study	367	43	11.7%
Ghaemi Nosrat et al [12]	927	109	11.76%
Dhananjay CD and Kiran B et al [13]	366	38	10.38%
N. Najati et al [11]	852	52	6.1%

In our study, we found a maximum number of preterm babies (56%) followed by term babies (44%) which is comparable with a Turkish study [14]. In the present study, there were no post-term deliveries. There was a male preponderance with a male-to-female ratio of 2:1 which is comparable with the recent Chinese and Indian studies [12,13] with a male-to-female ratio of 1.3:1 and 1.37:1 respectively.

Hypoglycemia can present without apparent symptoms, the so-called asymptomatic hypoglycemia found in neonates at risk of hypoglycemia. In our study, most babies (56%) had asymptomatic hypoglycemia which is comparable with an Indian study (59.3%) from Kerala [15]. Neonatal hypoglycemia can have a variable presentation. In our study jitteriness accounted for 57.9% of cases whereas a western study [16] noticed jitteriness in about 62.7% of cases. We noticed convulsions in about 26.3% of cases, whereas recent Western studies [16,17] noticed convulsions in about 37.5% and 16.6% respectively. Apneic spells in the present study (15.8%) were comparable with that of a Western study (17.3%) [16]. Lethargy constituted 42.1% of cases in our study which is relatively higher than the Western study (30%) [16].

There were various maternal risk factors for neonatal hypoglycemia. In the present study, we found that pregnancy-induced hypertension (PIH) was the most significant risk factor associated with hypoglycemia, accounting for 37.2% of cases, followed by Antepartum haemorrhage and chronic and gestational diabetes mellitus. Out of the all risk factors observed by recent Indian [15] and Western [12] studies, it was also seen that PIH was the most significant maternal risk factor associated with hypoglycemia accounting for about 16.5% and 15.62% of cases respectively. Out of the neonatal risk factors studied in the present study, we found that prematurity (55.8%) was the most significant

Risk factor followed by early onset sepsis (30.2%), birth asphyxia (27.9%), intrauterine growth restriction (IUGR) (13.9%) and large for gestational age (LGA) (6.9%). The risk factors studied by a Western study[12] have also shown that prematurity was the most significant risk factor accounting for about 43.1% of cases, followed by birth asphyxia, IUGR and sepsis. One recent Indian study [15] has shown that IUGR was the most significant risk factor accounting for about 29.6% of cases, followed by prematurity and birth asphyxia.

Symptomatic hypoglycemia should be treated with parenteral continuous glucose infusion. Breastfeeding is the initial management of asymptomatic hypoglycemia. Different units follow different protocols for the management of asymptomatic hypoglycemia. Many units resort to giving sugar-fortified feeds or supplementary formula feeds. The incidence of hypoglycemia varies according to the protocols and feeding methods. There is a paucity of data on the incidence of hypoglycemia where an exclusive breastfeeding policy is followed.

In the present study, 367 babies were screened for hypoglycemia out of which 43 (11.7%) were found to be hypoglycemic. Kaiser et al reported an incidence of hypoglycemia of 19.3% in 1395 newborns with gestational age between 23 and 42 weeks using a cut-off of <45 mg/dl [18]. The incidence is almost similar to our study. Other studies also documented much lower incidences due to universal screening. Smolkin et al reported a 5% incidence of hypoglycemia among 519 term newborns with no risk factors born by elective caesarean section below 35 mg/dl as cutoff [19].DePuy et al, using universal point-of-care glucose screening in 4892 full-term infants born to non-diabetic mothers weighing >2500 g during the first day of life, found only 2.4% of glucose levels below 50 mg/dl [20] Singh et al studied in Indian infants at risk of hypoglycemia and reported 27% incidence but the studied population size was small [21].

The incidence of hypoglycemia in preterm babies was 55,8%, which is higher than Singh et al and De et al study [22]. In Singh et al the incidence of hypoglycemia in preterm infants was 36.9% [21]. In the De et al study, the incidence of hypoglycemia was 77.7% in preterm babies [22] The reason for this may be due to the small

Size population included in their study. This is also because most of our preterm babies are high risk with morbidities like very low birth weight (<1500 grams), RDS etc., requiring NICU admission and hence not included in the present study.

Conclusion

Neonatal hypoglycemia constituted about 11.7% of NICU admissions. Persistent hypoglycemia was noted in 6.9% of cases. Identification of risk factors of hypoglycemia and proper monitoring of blood glucose levels should be done to plan early treatment and prevent neurological damage. So, newborns with risk factors for hypoglycemia should be screened at regular intervals for blood glucose levels more specifically at the first 24 hours of life to prevent hypoglycemia and potential neurodevelopmental damage.

Hypoglycemia in neonates can have variable presentations indicating the need for detailed and thorough examination for evidence of hypoglycemia. Identification of risk factors of hypoglycemia and proper monitoring of blood glucose levels should be done to plan early treatment and prevent neurological damage. Mandatory blood glucose screening in babies with any one of the above-mentioned risk factors serves as an easy and cost-effective measure for the prompt identification of this condition.

The risk factor associated with developing hypoglycemia was maternal hypertension, chronic and gestational diabetes mellitus and antepartum haemorrhage while early initiation of breastfeeding and the mother's colostrum are protective factors. Due to the high incidence of hypoglycemia in the premature population, we recommend providing glucose infusion as soon as possible after birth, and continued screening and treatment as per local hospital guidelines.

Author's contribution

Dr. Prerana Singh: Concept, study design, manuscript writing and statistical analysis.

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