

Original Research Article

Study of incidence, risk factors and immediate outcome of hypoglycemia in neonates admitted in NICU

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ABSTRACT

Background: Hypoglycemia is the most common metabolic problem occurring in newborns which is associated with poor neurologic outcome. The present study was conducted to determine the incidence, risk factors and immediate outcome of hypoglycemia in neonates.

Methods: The present study was conducted on 3776 babies born with risk factors for hypoglycemia in NICU. Screening for blood glucose level of study subjects were done at 2, 4, 6, 12, 24, 48, 72 hours of life, twice daily and whenever symptomatic by using glucometer. Babies were followed up till discharge. Incidence, risk factors and immediate outcome of hypoglycemia were assessed. Appropriate tests were applied.

Results: Incidence of hypoglycemia was 9.93% among high-risk neonates and overall incidence was 5.20%. 54.13% were males. 45% were preterm, 78.7% neonates were LBW. 53.07% were born to primiparous mother, 20.5% to diabetic mothers and 28.5% to hypertensive mothers. 16.8% had perinatal asphyxia, 14.66% new-born had underlying RDS. 48.5% were symptomatic, most common being lethargy 52.75% followed by jitteriness 43.41%, convulsion in 63 (34.62%). Preterm and LBW were significantly associated with mortality. Most common underlying comorbidities associated with deaths were sepsis (59.10%), RDS (45.46%), perinatal asphyxia (13.64%) and meconium aspiration syndrome (4.55%).

Conclusions: Neonates with one or more risk factors for hypoglycemia should be screened irrespective of symptoms within 72 hours of life. Focused counselling on early initiation of breast feeding will reduce the incidence of hypoglycemia and its complications.

Key Words: Neonates, Hypoglycemia, Incidence, Risk factors, Screening, Outcomes

INTRODUCTION

Hypoglycemia is the most common metabolic problem occurring in new-borns.¹ Hypoglycemia 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. This so-called operational threshold values are useful guidelines for clinicians to take appropriate actions. Till proper evidence is generated, this value is currently believed to be a blood

glucose value of less than 40 mg/dl (plasma glucose less than 45 mg/dl).² Neonatal hypoglycemia is important because it is a common disorder, which is associated with brain injury and poor neurologic outcome.³ Little evidence exists to guide treatment and repeated calls have been made to develop evidence-based guidelines for the treatment of neonatal hypoglycemia.⁴ It is of note that the worst neurological outcome in large number of children is observed in neonates and infants with persistent and recurrent severe hypoglycemia. Hypoxic ischaemic

encephalopathy is found in about 50% of patient of neonatal hypoglycemia.⁵ The risk factors for hypoglycemia are infant of diabetic mother, LGA (birthweight >90th percentile), SGA (birth weight <10th percentile), low birth weight (>1800 to <2500 grams) and preterm (35-37 weeks). The lower limit of fetal glucose concentration is around 54 mg/dl in most of gestation, particularly after 20 weeks. At birth, the blood glucose concentration of new-born is about 70% of the maternal level. It reaches rapidly to a nadir by 1 hour to a value as low as 20 to 25 mg/dl.⁶ In 2011, the American Academy of Pediatrics (AAP) revised hypoglycemia guidelines, defining the high-risk population for screening (i.e., late preterm newborns, small for gestational age (SGA), and infants of diabetic mothers) and advising intravenous glucose administration to symptomatic newborns with <40 mg/dl or any newborn with glucose levels <25 mg/dl. Routine monitoring of blood glucose is not advised in healthy new-borns.⁷ The present study was conducted to determine the incidence, risk factors and immediate outcome of hypoglycemia in neonates in NICU.

Objectives

Objectives of current study were to determine the incidence of hypoglycemia in neonates in NICU, to study risk factors and immediate outcome with hypoglycemia in neonates in NICU.

METHODS

The present prospective study was conducted on 3776 babies born with risk factors for hypoglycemia satisfying inclusion criteria (such as infants of diabetic mother) between October 2019 to September 2021 in Neonatal Intensive Care Unit, Paediatrics department, Dr. Vaishampayan Memorial Govt medical College, Solapur (Maharashtra). Neonates with small for gestational age, birth weight <10 percentile, Low birth weight babies, birth weight < 2500 grams, Large for gestational age (LGA) infants, birth weight >90 percentile, respiratory distress syndrome, sepsis and with perinatal asphyxia, Infants of diabetic mothers (IDM) maternal type 1 or type 2 diabetic mellitus or gestational DM, hypertensive mother were included. Neonates with congenital malformation were excluded. After taking informed consent from parents or relatives, clinical findings, socio demographic factors, and investigations of all enrolled neonates were taken. After taking Institutional Ethics Committee clearance data was collected by using a pre designed proforma which consisted of standard questions related to clinical condition, socio demographic factors, family history, and so on. Clinical examination, diagnosis, investigations details were studied. Screening for blood glucose level of study subjects were done at 2, 4, 6,12,24,48,78 hours of life, twice daily and whenever symptomatic by using glucometer (one touch select simple). Heel prick was made by using sterile disposable lancet, on the lateral aspect of heel, with aseptic precautions by using spirit swab to clean the site and allowing it to dry. Blood was allowed to flow,

without squeezing. Using dextrose reagent strips capillary blood glucose level was measured and recorded. Any value below 40 mg/dl was confirmed by serum glucose level in venous blood by Hexokinase Method. Values consistent with capillary blood glucose was taken as hypoglycemia for the purpose of study. Hypoglycemic babies confirmed by lab test were followed up till discharge. All data was collected and complied in Microsoft excel. Results of continuous (quantitative data) measurement were presented on Mean +/- SD (min-max) and result on categorical (qualitative data) measurements was presented in percentage and proportions (%). Comparison of qualitative variable was analysed by chi-square test. Wherever necessary between groups, comparison of quantitative variables was analysed by independent student t test according to distribution. A p value of 0.05 was taken as level of significance and was considered statistically significant. Data analysis was done using R Studio and open epi version 2.3.1.

RESULTS

Total 7210 neonates were admitted in NICU during study period. Out of which ,3776 neonates were having one or more risk factors for hypoglycemia and satisfying inclusion criteria were screened. Total 375 neonates were found to have hypoglycemia. Out of 3776 neonates with one or more risk factors for hypoglycemia 375(9.93%) were found to have hypoglycemia. Out of high-risk neonates, 3401 (90.07) were euglycemic. Incidence of hypoglycemia was 9.93%.

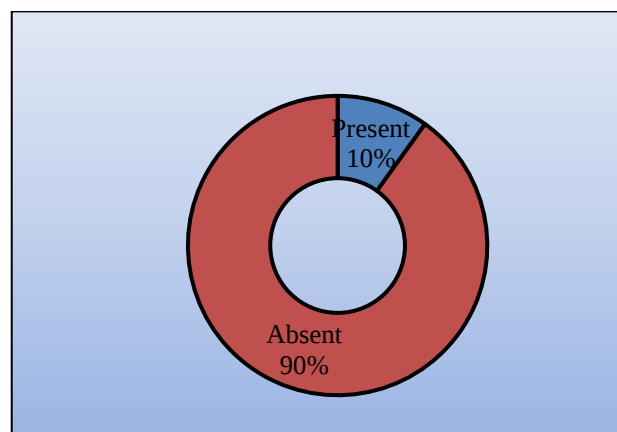


Figure 1: Incidence of hypoglycemia.

Baseline characteristics and clinical profile of the patients

Out of total 375 hypoglycemic neonates 203 (54.13%) were males and 172 (45.87%) were females. Higher incidence of hypoglycemia was seen among male neonates. 195 (52%) hypoglycemic neonates were born by normal vaginal delivery and 180 (48%) by Caesarean section. Majority of new-borns were preterm 169 (45.06%), 134 (35.73%) were term and 72 (19.21%) were post term. 169 (45.06%) were SGA, 145 (38.67%) were

AGA and 61 (16.27%) were LGA. Small for gestational age constituted maximum cases of neonatal hypoglycemia. Majority 163(43.5%) neonates had birth weight between 1.5 to 2.499 kgs, 132 (35.2%) had <1.5 kgs, 35 (9.3%) had 2.5 to 4 kgs and 45 (12%) had >4 kgs. 199 (53.07%) hypoglycemic neonates were born to primiparous mother whereas 176 (46.93%) were born to multiparous mother. (Table 1).

Table 1: Baseline characteristics and clinical profile of the patients.

Patient Variables		N	%
Gender	Male	203	54.13
	Female	172	45.87
Mode of delivery	Normal vaginal	195	52
	Caesarean section	180	48
Maturity of Neonate	Preterm	169	45.06
	Term	134	35.73
	Post term	72	19.21
Gestation age	AGA	145	38.67
	SGA	169	45.06
	LGA	61	16.27
Weight (Kgs)	<1.5	132	35.2
	1.5 to 2.499	163	43.5
	2.5 to 4	35	9.3
	>4	45	12
Parity of mother	Primiparous	199	53.07
	Multiparous	176	46.93
Diabetic mother	Yes	77	20.5
	No	298	79.5
Hypertensive mother	Yes	107	28.5
	No	268	71.5
Peri-natal Asphyxia	Yes	63	16.8
	No	312	83.2
Respiratory distress syndrome	Present	55	14.66
	Absent	320	85.34
Clinical symptoms	Asymptomatic	193	51.5
	Symptomatic	182	48.5
Presenting complaints	Lethargy	96	52.75
	Jitteriness	79	43.41
	Apnoeic spells	56	30.77
	Convulsion	63	34.62
Underlying sepsis	Yes	127	33.87
	No	248	66.13
Total		375	100

77 (20.5%) were born to diabetic mother and 298 (79.5%) were born to non-diabetic mother. 107 (28.5%) were born to hypertensive mothers and 268 (71.5%) were born to mother who had no history of hypertension. 63 (16.8%) had perinatal asphyxia and 312 (83.2%) had no perinatal asphyxia. Among all hypoglycemic new-born, 55 (14.66%) new-borns had underlying respiratory distress syndrome. 193 (51.5%) of neonates were asymptomatic and 182 (48.5%) hypoglycemic neonates were symptomatic. Among all 182 symptomatic hypoglycemic neonates most common clinical presentation were lethargy

96 (52.75%), jitteriness 79 (43.41%), convulsion 63 (34.62%) and apnoeic spells in 56 (30.77%).

Table 2: Details of hypoglycemia and in-hospital course of the patients.

Patient variables		N	%
Onset (hours)	≤48	224	59.7
	49-72	111	29.7
	>72	40	10.6
treatment required	Feeding only	74	19.73
	IV Dextrose	301	80.27
Steroids	Given	51	13.6
	Not given	324	86.4
NICU stay (days)	≤3	101	26.93
	>3	274	73.07
Total		375	100

127 (33.87%) had underlying sepsis and 248 (66.13%) had no sepsis. 224 (59.7%) had onset within 48 hours of life, 111 (29.7%) had onset within 49-72 hours and 40 (10.6%) had onset after 72 hours of life. Most of the hypoglycemic neonates had onset within 48 hours of life.

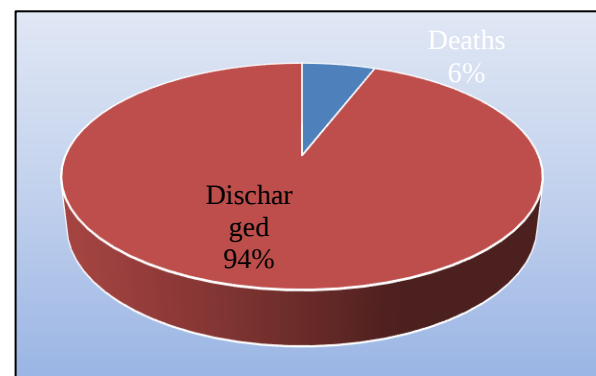


Figure 2: Distribution based on outcome of disease.

Majority 301 (80.27%) neonates required glucose infusion and 74 (19.73%) were managed only on feeds. 51 (13.6%) neonates required steroid and other 324 (86.4%) didn't require steroid for correction of hypoglycemia. Steroid required for neonates with resistant/recurrent episodes of hypoglycemia which were not controlled on glucose infusion. Total 101 (26.93%) were either discharged or died on or before 3 days of NICU stay and 274 (73.07%) required NICU stay for more than 3 days. In this study longer NICU stay was attributed to prematurity and low birth weight. (Table 2) shows, in this study out of total 375 hypoglycemic neonates 353 (94.13%) were discharged and 22 (5.87%) died due to underlying comorbidities. Out of 169 preterm, 152 (89.94%) were discharged and 17 (10.06%) died. Out of 134 term, 132 (98.51%) were discharged and 2 (1.49%) died and out of 72 post-term, 69 (95.83%) were discharged and 3 (4.17%) died, showed statistical significance. P value is 0.005. Out of 145 AGA, 132 (91.03%) were discharged and 13(8.97%) died. Out of 169 SGA, 161 (95.27%) were discharged and 8 (4.73%) died and out of 61 LGA, 60 (98.36%) were discharged and

1 (1.640%) died, showed no statistical significance, $p=0.08$. Out of 132 having weight <1.5 kgs, 117 (88.64%) were discharged and 15 (11.36%) died. Out of 163 having weight 1.5-2.449 kgs, 157 (96.32%) were discharged and

6 (3.68%) died. Out of 35 having weight 2.5-4 kgs, 35 (100%) were discharged and 0 died. out of 45 having weight >4 kgs, 44 (97.78%) was discharged and 1 (2.22%) died.

Table 3: Association of patient's risk factors and outcome of disease.

Patient's risk factors		Outcome		Total	Chi square, p value
		Discharged	Died		
Term of the neonates	Preterm	152	17	169	0.005*
	Term	132	2	134	
	Post	69	3	72	
Gestational age	AGA	132	13	145	0.08
	SGA	161	8	169	
	LGA	60	1	61	
Weight in kgs	<1.5	117	15	132	0.007*
	1.5 to 2.499	157	6	163	
	2.5 to 4	35	0	35	
	>4	44	1	45	
Total		353	22	375	

Distribution of death based on underlying neonatal comorbidities

Most common underlying comorbidities associated with deaths were sepsis 13 (59.10%), respiratory distress syndrome 10 (45.46%), perinatal asphyxia 3 (13.64%), meconium aspiration syndrome 1 (4.55%).

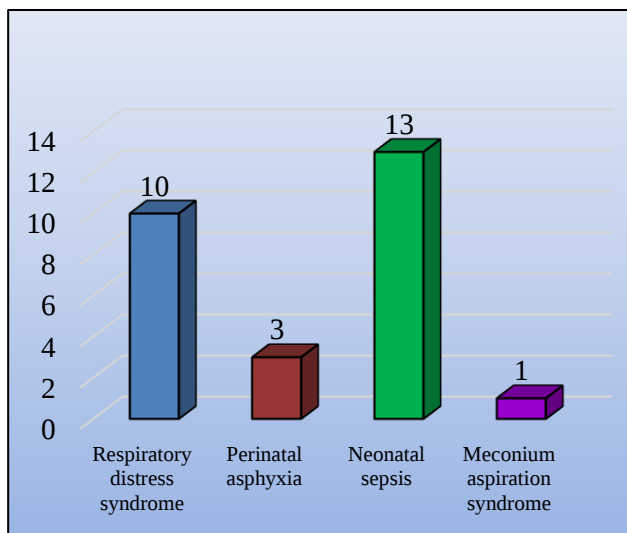


Figure 3: Deaths based on underlying neonatal comorbidities.

DISCUSSION

Incidence of hypoglycemia

Present study shows, total 375 neonates were found to have hypoglycemia. Incidence of hypoglycemia was 9.93% among high-risk neonates and overall incidence was 5.20%. In study conducted by Kumar et al 7808 babies

were live born, of these 1883 (24.1%) infants with one or more of the risk factors for hypoglycemia were screened.⁴ The incidence of hypoglycemia in newborns with risk factors was 627 (33.3%). In study by Dhananjaya et al showed that overall incidence of hypoglycemia was 4.2%.⁸ Hosagasi et al conducted a study and found that incidence of hypoglycemia was 16.6%. According to WHO Neonatal hypoglycemia is estimated to 1.3-3 per 1000 live births.⁹⁻¹¹ Other authors report an incidence between 7-11%.

Among hypoglycemic neonates

Gender: In our study out of total 375 hypoglycemic neonates 203 (54.13%) were males and 172 (45.87%) were females. Higher incidence of hypoglycemia was seen among male neonates. Results are comparable to study by Dhananjaya et al which showed that males were 22 (57.89%), females were 16 (42.10%). Babu et al showed that 57.5% were males and 42.5% were females. Burakevych et al showed that 66 (47%) were males.⁸⁻¹³ Mode of delivery: in our study (195) 52% hypoglycemic neonates were born by normal vaginal delivery and 180 (48%) by Caesarean section. Study conducted by Shah et al showed that majority were born by Caesarean Section.¹⁴ Kumar et al showed that the incidence of hypoglycemia in babies born by LSCS and Vaginal delivery were 41% and 16% respectively.⁷ Among 627 hypoglycemic neonates 533 (85%) were born by normal vaginal delivery and 94 (15%) by LSCS.

Thirumalaikumarasamy et al showed among hypoglycemic neonates 43.75% were born by LSCS and 56.25% were born by vaginal delivery.¹⁵ Maturity: In present study, majority of newborns were preterm 169 (45.06%), 134 (35.73%) were term and 72 (19.21%) were post term. In study by Dhananjaya et al showed that preterm -11.9%, term -2.9%. Stomnarosk O et al showed that 89.25% of the babies were premature.⁵⁻⁸ Kumar et al

showed that 19% of preterm.⁷ Burakevych et al showed that 35% were preterm.¹³ Babu et al showed that 57.5% were term and 42.5% were preterm.¹⁶

Gestational age: In present study, 169 (45.06%) were SGA, 145 (38.67%) were AGA and 61(16.27%) were LGA. In study by Dhananjaya et al showed that SGA-14.75%, LGA-22.22%.^{8,16} Bhand et al showed that 26% were small for gestational age.⁶ Stomnarosk et al showed that mean gestational age was 33.05±3.19 weeks.⁵ Kumar et al showed that 42% of SGA, 10% of LGA babies. Burakevych et al showed that 11 (8%) were born at 32-34 weeks' gestational age, 49 (35%) at 35-36 weeks' and 79 (57%) at term.⁷⁻¹³ Among neonates born at 35-36 weeks' gestation >80% of admissions to the NICU after birth was showed by Ishiguro et al.¹⁰

Birth weight: In our study majority 163 (43.5%) neonates had birth weight between 1.5 to 2.499 kgs, 132 (35.2%) had <1.5 kgs, 35 (9.3%) had 2.5 to 4 kgs and 45(12%) had >4 kgs. In study by Bhand et al showed that 49% had low birth weight.⁶ Shah et al showed that of 661 preterm babies (birthweight <1,850 g).¹⁴ Stomnarosk et al showed that mean birth weight was 1795.95 ±596.08 grams, out of 84 neonates with hypoglycemia 32 (38.08%) were very low birth weight (<1500 g), 38 (45.22%) were low birth weight (1500-2500g).⁵

Distribution based on parity of mother

In this study 199 (53.07%) hypoglycemic neonates were born to primiparous mother whereas 176 (46.93%) were born to multiparous mother, which is comparable to studies conducted by Kumar et al in which 394 (62.8%) were born to primiparous and 233 (37.2%) were born to multiparous mother.⁷ Amrendra et al and another study by Thirumalaikumarasamy et al showed (61%) and (42.8%) were born to primiparous and (39%) and (57.2%) were born to multiparous mother respectively.¹⁵

Co morbid mothers

In our study, out of 375 hypoglycemic neonates 77 (20.5%) were infant of diabetic mothers and 107 (28.5%) were born to hypertensive mothers. Dhananjaya et al showed that maternal risk factors contributed to the development of hypoglycemia were IGDM/IDM (40%), and eclampsia (40%).⁸ Hosagasi et al conducted a study and found that 12 cases had IDM (5.7%).¹ Kumar et al showed that 33% of IDM.⁷ Burakevych et al showed that 33% were IDM.¹³ Babu et al showed that 5% mothers had Diabetes mellitus, 10% had HTN, 32.5% had PIH.¹⁴⁻¹⁶

Neonatal risk factors

In our study among all hypoglycemic neonates, 63 (16.8%) had perinatal asphyxia and 312 (83.2%) had no perinatal asphyxia,⁵⁵ (14.66%) new-born had underlying respiratory distress syndrome. Out of 375 hypoglycemic neonates, 127 (33.87%) had underlying sepsis and 248

(66.13%) had no sepsis. Study by Dhananjaya et al showed birth asphyxia had highest incidence of 26.86% followed by RDS and septicaemia both 15%.⁸ In birth asphyxia, term babies were more prone to hypoglycemia with incidence of 61.11%. Study by Tiple et al showed that the most common neonatal risk factor associated with hypoglycemia was birth asphyxia in 46 (43.39%) neonates followed by RDS in 31 (29.24%) neonates, septicaemia in 20 (18.86%) neonates and meningitis in 9 (8.49%) neonates.¹⁸

Symptomatic

In this study 193 (51.5%) of neonates were asymptomatic and 182 (48.5%) hypoglycemic neonates were symptomatic. Among all 182 symptomatic hypoglycemic neonates most common clinical presentation were lethargy 96 (52.75%), jitteriness 79 (43.41%), convulsion 63 (34.62%) and apnoeic spells in 56 (30.77%). Study by Dhananjaya et al showed that 38 Newborn babies were hypoglycemic out of which 60% were asymptomatic and 40% were symptomatic.⁸ Kumar et al showed that 576 (91.9%) were asymptomatic hypoglycemia and 51 (8.1%) symptomatic hypoglycemia.⁷ Fluge et al reported five of seven asymptomatic children to be normal at a mean age of 3.5 years, although only one of nine symptomatic infants was normal.¹⁹ Singh et al observed 107 babies, symptomatic hypoglycaemia was found in 43 while 64 were asymptomatic.²⁰

Onset of hypoglycemia

In this study, out of 375 hypoglycemic neonates 224 (59.7%) had onset within 48 hours of life, 111 (29.7%) had onset between 49-72 hours and 40 (10.6%) had onset after 72 hours of life. Most of the hypoglycemic neonates had onset within 48 hours of life. Study by Somanathan et al showed the time for detection of hypoglycemia in newborn were 2-6 hours in 7 (7.7%), 6-12 hours in 20(9.1%), 12-24 hours in 27 (12.3%), 24-48 hours in 59 (26.8%), 48-72 hours in 47 (21.4%) and >72 hours in 50 (22.7%) of cases.²¹ In study by Amrendra et al incidence of hypoglycemia according to day of life was 31 (86.11%) on the first day, 4 (11.12%) on the second day, 2 (5.56%) on the third day of life.¹⁷

Management of hypoglycemia

In this study, majority 301 (80.27%) neonates required glucose infusion and 74 (19.73%) were managed only on feeds. 51 (13.6%) out of 375 hypoglycemic neonates requiring higher glucose infusion rate were given steroid for resistant/recurrent hypoglycemia. Study by Burakevych et al showed that 18% were treated only on feeds, 17% on formula, 23% with dextrose gel and breast milk.¹³ In study by Somanathan et al it was reported that out of 220 neonates with hypoglycemia, 159 (72.3%) neonates required oral feeds for the correction of hypoglycemia, 60 (27.3%) required IV dextrose and 1 (0.5%) neonate required hydrocortisone.²¹

NICU stay

In this study total 101 (26.93%) were either discharged or died on or before 3 days of NICU stay and 274 (73.07%) required NICU stay for more than 3 days. Similar study conducted by Somanathan et al showed out of 220 newborns with hypoglycemia, 208 (83.7%) required NICU stay for less than 3 days as most of them 159 (72.3%) required oral feed for correction of hypoglycemia and 36 (16.3%) required stay for more than 3 days. In our study longer NICU stay was attributed to prematurity and low birth weight.²¹

Final outcome

In this study, out of total 375 hypoglycemic neonates 353 (94.13%) were discharged and 22 (5.87%) died due to underlying comorbidities. Stomnarosk et al reported that overall mortality was 2.38% Singh et al showed that out of 153 neonates who experienced a single episode of hypoglycemia, 138 neonates (90.2%) were discharged while the remaining 15 neonates (9.8%) died.^{5,22} The overall mortality remains high, especially in children with co-morbidities. HIE and infections are the most common leading causes of death. The mortality rates ranged between 9 and 14.7%, Tiple et al reported that out of total 106 neonates with hypoglycemia, mortality was 19 (17.9%).^{9,18}

Association between risk factors and outcomes

Pre-term and lower weight were significantly associated with mortality (both p values <0.05). Most common underlying comorbidities associated with deaths were sepsis 13 (59.10%), respiratory distress syndrome 10 (45.46%), perinatal asphyxia 3 (13.64%), meconium aspiration syndrome 1 (4.55%). Similar studies by Somanathan et al reported the cause of neonatal mortality were birth asphyxia in 2 cases (33.3%), extreme prematurity with RDS in 2 cases (33.3%), sepsis in 1 (16.7%), meconium aspiration syndrome in 1 (16.7%).²¹ Another study by Tiple et al reported most common cause of death among hypoglycemic neonates were birth asphyxia in 9 (47.37%), RDS in 4 (21.05%), septicemia in 3 (15.79%).¹⁸

Limitations

True incidence couldn't be calculated as only neonates with one or more risk factors were screened. Newborn admitted for just phototherapy were not screened periodically. Those admitted from outside hospital initial records were not available for few patients so exact onset of hypoglycemia was not known in such cases. Delayed transportation from outside hospital and IV Dextrose given initially could have missed actual onset of hypoglycemia in such patient. Only short term outcome was studied, long term neurological outcome couldn't be studied.

CONCLUSION

Neonatal hypoglycemia constituted about 5.20% of all NICU admissions and 9.93% among high-risk neonates with one or more risk factors for hypoglycemia. Hypoglycemia in neonates have variable presentation, indicating the need for detailed and thorough examination for evidence of hypoglycemia. Neonatal mortality was 5.87 %. Neonatal mortality was correlated with lower birth weight, maturity and gestational age. Thus, high risk neonates with one or more risk factors for hypoglycemia should be screened for hypoglycemia irrespective of symptoms within 72 hours of life, so that early intervention can reduce neonatal mortality. It is strongly recommended the need for comprehensive team approach in the efforts to lower the rates of prematurity, low birth weight, perinatal asphyxia and infection. Many cases become euglycemic only with oral feeds. Hence focused counselling on early initiation of breast feeding will reduce the incidence of hypoglycemia and its complications.

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Ethical approval: The study was approved by the Institutional Ethics Committee

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