

## A STUDY ON ETIOLOGY, AGE AT ONSET, CLINICAL SPECTRUM AND SHORT TERM OUTCOME OF NEONATAL HYPOGLYCEMIA IN A TERTIARY CARE

B.S. Chakravarthy<sup>1</sup>, A. Satyavani<sup>2</sup>, V.Sindhura<sup>3</sup>, K. Satyakumari<sup>2</sup>, M.S. Raju<sup>4</sup>, Taru Prasanthi<sup>5</sup>, M.Lakshmi Soundarya<sup>6</sup>

Received : 11/11/2023  
Received in revised form : 18/12/2023  
Accepted : 02/01/2024

**Keywords:**

GDM, Hypoglycemia, Hyperinsulinemia, Newborns, Glucose.

Corresponding Author:

**Dr. K. Satyakumari,**

Email: drsatyamrsvalluri@gmail.com

DOI: 10.47009/jamp.2024.6.1.24

Source of Support: Nil,  
Conflict of Interest: None declared

*Int J Acad Med Pharm*  
2024; 6 (1); 125-130



<sup>1</sup>Professor, Department of Pediatrics, AMC, Vishakapatnam, Andhra Pradesh, India.

<sup>2</sup>Associate Professor, Department of Pediatrics, AMC, Vishakapatnam, Andhra Pradesh, India.

<sup>3</sup>Assistant Professor, Department of Pediatrics, AMC, Vishakapatnam, Andhra Pradesh, India.

<sup>4</sup>Professor & HOD, Department of Pediatrics, AMC, Vishakapatnam, Andhra Pradesh, India.

<sup>5</sup>Senior Resident, Department of Pediatrics, AMC, Vishakapatnam, Andhra Pradesh, India.

<sup>6</sup>Post Graduate, Department of Pediatrics, AMC, Vishakapatnam, Andhra Pradesh, India.

### Abstract

**Background:** To study the etiology and age at onset of neonatal hypoglycemia among different risk categories. To study the clinical spectrum and short term outcome of neonatal hypoglycemia. **Materials and Methods:** This study was a hospital based observational study conducted in tertiary care hospital, from March 2021 to August 2022. From all the parents of the neonates enrolled in the study, written informed consent was taken. All neonates admitted in NICU were screened at the time of admission. High risk neonates like preterm babies, SGA babies, LGA babies, IDM babies, those with birth asphyxia, etc., were screened at 2,4,6,12,24,48 & 72 hours as per the protocol. **Result:** In the present study, most (61.5%) of the hypoglycemic newborns were term, and majority have birth weight between 2-3 kg (37.6%). Among these 130 hypoglycemic newborns 53.8% were males & 46.2% were Females. Majority of the hypoglycemic newborns were appropriate for GA (71.5%). In the present study, most common maternal risk factor observed in hypoglycemic newborns was PIH (36.1%) followed by GDM (25.3%). Most of the hypoglycemic episodes occurred during first 24 hrs (63%) in all preterm, SGA, AGA and LGA infants. In the present study, sepsis (59.2%) was the most common etiology observed in these hypoglycemic newborns, followed by prematurity (38.4%). Most of the babies having asymptomatic hypoglycemia responded to oral feeds; any recurrences in these babies were treated with IV dextrose. Babies having asymptomatic hypoglycemia who did not respond to oral feeds initially were given. Most of the babies having symptomatic hypoglycemia (68.8%) initially responded to an IV glucose rate of 6mg/kg/min. Recurrence in these babies was treated with high concentrations of IV glucose. In the present study Recurrence was observed in 43.07% (56) of hypoglycemic newborns, of them 38.4% were given glucose infusion & 4.61% were treated with steroids along with IV dextrose. Of them one case had refractory hypoglycemia, found to have hyperinsulinaemia and was treated with diazoxide. Out of the 130 hypoglycaemic infants, 111 (85.3%) were discharged and 19 (14.6%) died. Common causes of death include sepsis, followed by RDS & birth asphyxia. **Conclusion:** Blood glucose screening in neonates with this risk factor is mandatory as many of the neonates were asymptomatic. The importance of early initiation of breast feeding to prevent hypoglycemia should be emphasized.

## INTRODUCTION

Neonatal hypoglycemia is a common problem during the initial hours to days following birth, in the newborn nurseries. In both well babies and sick babies who are at risk of hypoglycemia, this is one of the most common metabolic problem. In neonates, during the first few hours of life blood glucose

concentrations are typically lower than the normal values in older children and adults. Mostly neonatal hypoglycaemia has excellent prognosis as it is transient and responds readily to treatment. There is a high risk of severe neuro disability in patients with symptomatic hypoglycaemia. Persistent low glucose levels in babies should be investigated for an underlying cause.<sup>[1]</sup> Normal neurological function

and development needs blood glucose, hence prolonged low levels of blood glucose in newborns may result in recurrent seizure activity, irreversible brain damage, personality disorders and finally may result in death.<sup>[2]</sup>

However, the incidence of hypoglycaemia changes with definition and the population studied.<sup>[2]</sup> Overall incidence is 1-5/1000 live births.<sup>[2]</sup> Highest risk for hypoglycaemia (<46.8mg/dl) is for late preterm (54%), followed by SGA infants (52%) & IDM's (48%) & LGA infants (47%) according to a recent prospective study of infants at risk for hypoglycaemia.<sup>[1]</sup>

Neonatal hypoglycaemia is a subject to be reexplored as there are many controversies existing over the best way of detection of hypoglycemia. Despite the advances in neonatal care and increased institutional deliveries, the relation between plasma glucose levels, clinical symptoms and long term sequelae is poorly understood. Hence this study was taken up to find out the causes of neonatal hypoglycemia in the neonatal intensive care unit and to study the clinical profile and outcome (discharged/death) of hypoglycemia in neonates.

This study was conducted in a tertiary care hospital, in which high risk newborns were screened for hypoglycemia by point of care glucometer device, blood sugar  $\leq$  45mg/dl was taken as cut off for hypoglycaemia and were screened for hypoglycaemia at 2,6,12,24,48 & 72 hours. Age at onset of hypoglycaemia and duration of treatment required for hypoglycaemia is obtained.

#### **Aims & Objectives**

1. To study the etiology and age at onset of neonatal hypoglycemia among different risk categories.
2. To study the clinical spectrum and short term outcome of neonatal hypoglycemia.

## **MATERIALS AND METHODS**

**Study place:** Neonatal Intensive Care Unit, Department of paediatrics, King George Hospital, Andhra Medical College, Visakhapatnam.

**Study population:** Newborn babies admitted (both inborn & outborn) in NICU of King George Hospital, during study period with risk factors for developing hypoglycaemia.

**Study Period:** 1<sup>st</sup> March 2021 to August 2022

**Sample Size:** 130

#### **Inclusion Criteria**

All neonates who had hypoglycaemia at admission or during NICU stay both inborn and outborn were enrolled in the study.

#### **Exclusion Criteria**

Neonates with lethal congenital malformations.  
Neonates who expired within 24 hrs of admission in NICU.

**Methodology:** This study was a hospital based observational study conducted in tertiary care hospital, from March 2021 to August 2022. From all the parents of the neonates enrolled in the study,

written informed consent was taken. All neonates admitted in NICU were screened at the time of admission. High risk neonates like preterm babies, SGA babies, LGA babies, IDM babies, those with birth asphyxia, etc., were screened at 2,4,6,12,24,48 & 72 hours as per the protocol. Those babies who had hypoglycaemia on screening were enrolled in the study. For all enrolled cases maternal details like PIH, GDM, Anaemia, oligohydramnios, etc., were noted. Baby details like birth weight, GA, birth asphyxia, NNT, sepsis, RDS, etc., were noted and protocol treatment for hypoglycaemia was initiated. The babies were followed throughout their hospital stay and any complications during the hospital stay were noted.

Blood glucose was screened immediately using a one-touch glucometer device. After thorough hand washing, the sole of the newborn baby was pricked with a sterile lancet.

The strength of these currents depends on the amount of glucose in the blood sample. According to the manufacturer, the test is linear up to 33.3 mmol/L (600 mg/dL). This method measures glucose levels down to 1.1 mmol/L (20 mg/dL).

For babies with blood glucose <40 mg/dl, a second blood sample was immediately sent to the laboratory to measure total blood glucose, and hypoglycemia was managed according to standard treatment protocols. In addition, in some cases, samples were sent for relevant investigations from a diagnostic and management perspective, depending on the case.

Asymptomatic infants were given oral feedings and blood glucose levels were tested 30 minutes later. If the repeated blood glucose value was < 40 mg/dl, an IV glucose infusion was started at 6 mg/kg/min. Depending on response and recurrence, the infusion rate was increased from 6 mg/kg/min to 12mg/kg/min at the rate of 2mg/kg/min. If unresponsive to IV glucose they are treated with drugs such as hydrocortisone.

Symptomatic infants were given an intravenous (IV) bolus of 2 ml/kg of 10% dextrose, followed by glucose infusion at 6mg/kg/min. Blood sugar was again checked after 30min. If the blood sugar levels are maintained >40mg/dl, then the sugar levels are monitored every two hours. After 24 hrs of IV glucose infusion, if two glucose values are observed >40mg/dl, the infusion is tapered at the rate of 2mg/kg/ min every six hours along with blood sugar monitoring. Tapering of infusion is accompanied with concomitant increase in oral feeds. Once the glucose infusion rate reached 4mg/kg/min, oral feeding is adequate and glucose levels maintained >40mg/dl, glucose infusion was stopped. In case of refractory hypoglycaemia (nonresponsiveness to glucose infusion of 12mg/kg/min), hydrocortisone, octreotide, diazoxide were used. All these details were entered in the proforma.

For all the babies who had hypoglycaemia, the time of onset of hypoglycaemia, duration of hypoglycaemia, glucose drip rate required and the final outcome in terms of discharge/ death were noted

**Statistical Analysis:** Clinical and biochemical data was tabulated. Qualitative data was presented as frequency and percentage according to their distribution. Data was analysed with the IBM SPSS version 21.0.

## RESULTS

All neonates who had hypoglycemia at admission or during NICU stay both inborn and outborn, were enrolled in the study.

In the present study, out of 130 babies, 3.8% (n=28) have weight <1 kg, 21.5% (n=28) have weight between 1-2 kg, 37.6% (n=49) have weight between 2-3 kg and 36.9% (n=48) have weight >3kg. [Table 1] Among 130 hypoglycaemic infants studied, 26 newborns were early preterm, 24 newborns were late preterm & 80 newborns were term. [Table 2]

Among 130 hypoglycaemic infants studied, 18 (13.8%) were SGA, 93 (71.5%) were AGA & 19 (14.6%) were LGA. [Table 3]

Out of 130 hypoglycaemic newborns, 25 babies (19.2%) were delivered through caesarean section & 105 (80.7%) were delivered vaginally. [Table 4]

In the present study, among the 130 newborns studied, mothers of 47 (36.1%) newborns had PIH, mothers of 33 (25.3%) newborns had GDM, 6 (4.6%) mothers had anaemia, 3 (2.3%) had oligohydramnios & 2 (1.5%) mothers had other risk factors like TORCH infections during their antenatal period. [Table 5]

In the 130 hypoglycaemic newborns studied, the comorbidity most commonly associated with hypoglycaemia is NNJ which is observed in

99 (76.1%) newborns, followed by sepsis 77 (59.2%), birth asphyxia 40 (30.7%), and RDS 33 (25.3%). [Table 6]

During the study, most neonates 49 (37.6%) were asymptomatic during the episode of hypoglycaemia, 19 (14.6%) neonates presented with lethargy, 18 (13.8%) neonates had seizures, 14 (10.7%) neonates presented with refusal of feeds, 10 (7.6%) neonates had apnea, 8 (6.1%) neonates had jitteriness, 6 (4.6%) presented with high pitched cry, 5 (3.8%) had hypotonia & 1 neonate presented with tachypnoea. [Table 7]

Among the 130 hypoglycaemic neonates, 50 were preterm, most of them 26 (20%) presented in the first 24 hrs, 22 (16.9%) newborns presented between 24-72 hrs, 2 (1.53%) newborns presented after 72 hrs. 18 were SGA, most of the SGA newborns 12 (9.23%) presented in the first 24 hrs, 6 (4.61%) newborns presented in between 24-72 hrs. 19 were LGA, most of the LGA newborns 16 (12.3%) also presented in the first 24 hrs, 2 (1.53%) of them presented in 24-72 hrs, 1 (0.76%) of them presented after 72 hrs. [Table 8]

Of the 130 hypoglycaemic neonates, 37 (28.4%) responded to oral feeds, 93 (71.5%) responded to IV dextrose, 5 (3.8%) of all the neonates with recurrent hypoglycaemia responded to drugs like steroids & one neonate (0.7%) had hyperinsulinaemia who responded to diazoxide. [Table 9]

Of all the 48 newborns who were given oral feeds during the episode of hypoglycaemia, 37 (77%) of them responded to oral feeds, but 4 among them had recurrence and was treated with IV dextrose and 11 (23%) of them did not respond to oral feeds and they were given IV Dextrose. [Table 10]

**Table 1: Distribution of study population by birth weight**

Birth weight	Frequency	%
< 1 kg	5	3.8%
1-2 kg	28	21.5%
2-3 kg	49	37.6%
>3 kg	48	36.9%

**Table 2: Distribution of Study population by GA**

Gestational age	Frequency	Percentage
>37 wks	80	61.5%
34-36 wks	24	18.4%
28-34 wks	26	20%

**Table 3: Distribution of Study population by wt for GA**

Wt for GA	Frequency ( n = 130 )	Percentage
SGA	18	13.8%
AGA	93	71.5%
LGA	19	14.6%

**Table 4: Mode of Delivery**

Mode of Delivery	Frequency	Percentage
LSCS	25	19.2%
VD	105	80.7%

**Table 5: Maternal risk factors**

Maternal risk factors	Frequency	Percentage
PIH	47	36.1%
GDM	33	25.3%

ANAEMIA	6	4.6%
OLIGOHYDRAMNIOS	3	2.3%
OTHERS	2	1.5%

**Table 6: Comorbidities of Hypoglycaemia.**

Comorbidities	Frequency	Percentage
Birth Asphyxia	40	30.7%
RDS	33	25.3%
NNJ	99	76.1%
Sepsis	77	59.2%

**Table 7: Clinical presentation of Hypoglycaemia**

Clinical presentation	Frequency	Percentage
Asymptomatic	49	37.6%
Lethargy	19	14.6%
Seizures	18	13.8%
Refusal of feeds	14	10.7%
apnoea	10	7.6%
Jitteriness	8	6.1%
High pitched cry	6	4.6%
Hypotonia	5	3.8%
Tachypnoea	1	0.7%

**Table 8: Age of onset of hypoglycaemia versus cause of hypoglycaemia**

S. No	Cause of hypoglycaemia		< 24 hrs	24– 72 hrs	>72 hrs	Total
1.	Preterm		26 (20%)	22 (16.9%)	2(1.53%)	50
2.	SGA		12 (9.23%)	6 (4.61%)	0	18
		Term	4 (3.07%)	0	0	4
		Preterm	8 ( 6.15%)	6 (4.61%)	0	14
3.	AGA		54 (41.5%)	35(26.9%)	4(3.07%)	93
		Term	37 (28.46%)	20(15.3%)	2 (1.53%)	59
		Preterm	17 (13.07%)	15(11.5%)	2 (1.53%)	34
4.	LGA		16(12.3%)	2(1.53%)	1(0.76%)	19
		Term	15 (11.53%)	1(0.76%)	1(0.76%)	17
		Preterm	1 ( 0.76%)	1(0.76%)	0	2

**Table 9: Management of hypoglycaemia.**

Management	Frequency
Oral feeds	37
IV fluids (Dextrose)	93
Steroids	5
Diazoxide	1

**Table 10: Response to oral feeds**

Oral feeds	Frequency (n = 48)	Percentage
Responders	37	77%
Non responders	11	23%

**Table 11: IV Dextrose drip rate required**

Drip rate (mg/dl)	Frequency (symptomatic)	Frequency (asymptomatic)
6	64(68.8%)	5 (5.37%)
8	13 (13.9%)	3 (3.22%)
12	5 (5.37%)	3 (3.22%)

**Table 12: Treatment of recurrent hypoglycaemia**

Recurrent hypoglycaemia treated with (n= 56)	Frequency:	Percentage:
Glucose infusion	50	89.2%
Drugs	6	10.7%

**Table 13: Outcome of neonatal hypoglycemia**

Outcome	Frequency	Percentage
Discharge	111	85.3%
Death	19	14.6%

Of the 93 newborns who were treated with IVF during the episode of hypoglycaemia, 11 were asymptomatic, among them 5 (5.37%) required drip rate of 6mg/kg/min, 3 (3.22%) required drip rate of 8

mg/kg/min and 3 (3.22%) required drip rate of 12mg/kg/min. Remaining were symptomatic, of them 64 (68.8%) required drip rate of 6mg/dl, 13

(13.9%) of them required drip rate of 8 mg/dl & 5 (5.37%) of them required drip rate of 12mg/dl.

Those who were asymptomatic with blood glucose levels between 20-40mg/dl were given a trial of oral feeds. Newborns who did not respond to oral glucose and babies with asymptomatic hypoglycaemia with blood glucose levels are less than 20mg/dl & those with symptomatic hypoglycaemia were treated with IV dextros. Out of 93 neonates who were treated with IV dextrose, recurrent episodes of hypoglycaemia were observed in 56 neonates. [Table 11]

Of all the 56 neonates who had recurrent episodes of hypoglycaemia, 50 were treated with glucose infusion & 6 of them were treated with drugs.

Of all the cases with recurrent hypoglycemia, 43 were symptomatic hypoglycemic newborns who responded initially to IV dextrose, 11 were asymptomatic hypoglycemic newborns of them 5 responded to oral feeds initially & 8 did not respond to oral feeds initially & were given IV dextrose.

Refractory hypoglycaemia: One case had refractory hypoglycaemia even after starting steroids, critical sample was taken, found to have hyperinsulinaemia (2.9mcU/ml). The baby was started on diazoxide, then gradually the baby recovered and was discharged. [Table 12]

Out of the 130 hypoglycaemic infants, 111 (85.3%) were discharged and 19 (14.6%) died due to co morbidities like sepsis (15/19), followed by HMD(11/19) & birth asphyxia(11/19). [Table 13]

## DISCUSSION

Hypoglycemia is the most common metabolic disorder in newborns. If not recognized in time, it can lead to significant morbidity and mortality. Both symptomatic and asymptomatic hypoglycemia can lead to long-term neurological consequences. Therefore, appropriate and timely management is required to prevent brain injury in developing neonates. As such, there is no universally accepted point-of-care (POC) method for accurately and reliably determining blood glucose levels to use as the sole method of screening for hypoglycemia in at-risk neonates. The collection and processing of blood samples for analysis of glucose concentrations is also highly variable, with correspondingly different incidence rates.

Out of 130 hypoglycaemic newborns in the present study, the birth weight of 37.6% was in between 2-3 kg, 36.9% was more than 3kg, 21.5% was in between 1-2 kg and 3.8% was less than 1 kg. This is in contrast to the study done by orhideja stomnaroskal et al, in which more number of hypoglycaemic newborns weighed between 1.5-2.5 kg (54.3%), followed by less than 1.5 kg (34.2%), followed by 2.5- 3.5 kg (10.5%) & more than 4 kg (0.81%).

In the present study, 13.8% were SGA, 71.5% were AGA (of them 26.1% were preterm & 46.1% were term) and 14.6% were LGA. In a study done by Saini et al,<sup>[3]</sup> 41.7% of hypoglycemic newborns were AGA

and 58.3% were SGA, which has a p-value of 0.021 with a significant difference. Study by Tenovuo A et al,<sup>[4]</sup> in 1988 concluded that there is a five-fold risk for hypoglycemia which in SGA newborns.

In the present study, out of 130 hypoglycaemic neonates 80.7% were born through vaginal delivery & 19.2% delivered through caesarean section. These findings are similar to the study done by Amy M. DePuy et al,<sup>[5]</sup> in which 62.1% of hypoglycemic neonates were born through vaginal delivery. In the present study, among the 130 newborns studied, most of the mothers of newborns 47(36.1%) had PIH, mothers of 33(25.3%) newborns had GDM, 6 (4.6%) mothers had anaemia, 3(2.3%) had oligohydramnios & 2(1.5%) mothers had other risk factors like TORCH infections during their antenatal period. This is in contrast to study by Dr Rafiq Anjum et al,<sup>[6]</sup> (in which 38% mothers had GDM, 22% mothers had eclampsia, 9% mothers had a family history of metabolic disorder and 30% mothers had history of drug usage) and Somanathan S et al,<sup>[7]</sup> (18.6% mothers had GDM/overt DM, 10.9% mothers had PIH, 0.9% mothers had PROM > 18 hours).

In the present study, NNJ is most commonly associated with hypoglycemia which is observed in 99(76.1%) newborns, followed by sepsis 77(59.2%), birth asphyxia 40(30.7%) and RDS 33(25.3%). In a study done by Somanadhan S et al,<sup>[7]</sup> comorbidities were present in 16.3% of the hypoglycaemic neonates. Among them birth asphyxia was present in 12(5.4%), sepsis in 19(8.6%), polycythemia in 4 (1.8%) & shock in 1(0.45%), which is in contrast to the present study.

In the present study, most neonates 49(37.6%) were asymptomatic during the episode of hypoglycaemia. 19 (14.6%) neonates presented with lethargy, 18 (13.8%) neonates had seizures, 14(10.7%) neonates presented with refusal of feeds, 10(7.6%) neonates had apnea, 8(6.1%) neonates had jitteriness, 6(4.6%) presented with high pitched cry, 5(3.8%) had hypotonia & 1 neonate presented with tachypnoea. This is in contrast to study done by Dr Rafiq et al 6, in which the clinical presentation of hypoglycaemia is as follows - jitteriness in 34 (34%), cyanosis in 12(12%), tachypnoea in 8 (8%), apnoea in 6 (6%), temperature instability in 39 (39%), seizures in 9 (9%) and lethargy in 32 (32%).

In the present study, in 49 newborns asymptomatic hypoglycemia is identified. This is due to routine & periodic screening of all hypoglycemic newborns during their NICU stay. Identification of hypoglycemia in these asymptomatic newborns is particularly important in order to prevent adverse neurological outcome.

In the present study, most of the newborns 82(63%) presented in the initial hours of life (24 hrs) with hypoglycaemia, 43(33%) newborns had hypoglycaemia in 24-72 hrs & 5(3.8%) newborns had hypoglycaemia after 72 hrs of life.

Among the 130 hypoglycaemic neonates, 50 were preterm, most of them 27(54%) presented in the initial 24 hrs, 21 (42%) newborns presented between

24- 72 hrs and 2 (4%) newborns presented after 72 hrs. 17 were SGA, most of the SGA newborns 11(64.7%) presented in the initial 24 hrs, 6(35.2%) newborns presented between 24-72 hrs. 19 were LGA, most of the LGA newborns 16(84.2%) also presented in the initial 24 hrs, 2 (10.5%) of them presented between 24-72 hrs and 1 (5.26%) of them presented after 72 hrs.

This was similar to a study done by Somanathan S et al,<sup>[7]</sup> out of 220 neonates, hypoglycemia was detected in the first 24 hours in 29% of the newborns, 26.8% was detected in day 2 of life, 21.4% was detected in day 3 of life and 22.7% were found to be hypoglycaemic after 72 hours.

In the symptomatic group, the majority (49.2%) responded to the infusion rate of 6mg/kg/min. Of the rest, 10% responded to 8mg/kg/min, 3.84% responded initially to an infusion rate of 12mg/kg/min. Recurrences in these babies were managed with either higher concentrations of glucose or drugs. 2.3% of the total symptomatic group had persistent hypoglycemia, which was treated with drugs like hydrocortisone and diazoxide.

Incidentally, it was also found that babies with hypoglycemia who initially responded to higher drip rates of dextrose had more incidence of persistent hypoglycemia.

This is in contrast to the study done by Somanadhan et al,<sup>[7]</sup> in which 72.3% responded to oral feeds, 27.3% required intra venous dextrose & 0.5% required hydrocortisone.

This is somewhat similar to the study by Singh et al<sup>8</sup>, which showed that 34% of hypoglycaemic newborns required oral feeds, 66% required intravenous dextrose. In the present study, out of a total of 130 hypoglycemic babies, 43% had a recurrence. This is in contrast to a study done by Singh K et al,<sup>[8]</sup> in which recurrence was noted in 23.5% of the babies.

In the present study, 85.3% of babies were discharged and 14.6% of babies expired due to co morbidities like sepsis(15/19), followed by HMD(11/19) & birth asphyxia(11/19). . This is in contrast to the study done by Dedek I.O.F et al,<sup>[9]</sup> where 33.33% of hypoglycemic neonates expired.

In a study done by Singh K et al,<sup>[8]</sup> out of 153 neonates who experienced a single episode of

hypoglycemia, 90.2% (138) were discharged and remaining 9.8% (15) died. Out of 47 neonates with more than 1 episode of hypoglycemia, 85.1% (40) were discharged while the remaining 14.9% (7) died.

## CONCLUSION

The incidence of neonatal hypoglycemia was 14.6% among NICU admissions. The maternal risk factors associated with neonatal hypoglycemia were GDM, PIH, PROM and the neonatal risk factors were prematurity, SGA, LGA and comorbid conditions which include perinatal asphyxia, sepsis, polycythemia, shock. Since most of the neonates with hypoglycemia were asymptomatic. Among the symptomatic neonates poor feeding was the most common symptom on presentation and most of them achieved euglycemia with oral feeds.

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