

Original Research Article

Clinico-biochemical profile of hypoglycemia in neonates admitted in NICU

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ABSTRACT

Background: In high risk neonates' incidence of hypoglycemia is up to 30%. There is limited evidence-based consensus regarding screening and management of neonates at risk of hypoglycemia. This study was undertaken to know the incidence, clinical profile, sequential blood glucose level upto 72 hours and short-term outcome of neonatal hypoglycemia.

Methods: Blood sugar was screened at admission, after feed or D10 bolus, 6, 12, 24, 48 and 72 hours of age. Detailed maternal history and neonatal history, clinical manifestation, management and short-term outcome of hypoglycemic neonates were noted. Statistical analysis of data was done by SPSS 22.0 software.

Results: 200 neonates with blood glucose less than 40mg/dl at admission to NICU in which 47 had repeat episode of hypoglycemia. Incidence of hypoglycemia at admission was 22.49% and 5.29% was incidence of repeat episode of hypoglycemia. Pre-term ($p=0.005$), low birth weight ($p=0.020$) and SGA ($p=0.012$) had repeat episode of hypoglycemia. GDM ($p=0.040$), birth asphyxia ($p=0.046$) and early septicemia ($p=0.0001$) were common risk factors for hypoglycemia. Poor feeding, jitteriness and respiratory abnormality were common presentation of hypoglycemic neonates. The blood glucose levels at admission were less than 30 mg/dl in neonates who later had repeat episode of hypoglycemia. Most hypoglycemic episode after admission occurred within 24 hours of life.

Conclusions: LBW especially Preterm SGA neonates are at increased risk of hypoglycemia. Maternal and neonatal risk factors are GDM and birth asphyxia, early septicemia. Screening for hypoglycemia is essential for high-risk neonates.

Keywords: Hypoglycemia, Low birth weight, Pre-term, Small for gestational age

INTRODUCTION

Glucose is essential for all mammalian cells and it is a primary source of energy for brain. Neonatal hypoglycemia is one of the most common biochemical abnormalities encountered in the newborn. Decrease in glucose level of the circulating blood is termed as hypoglycemia. The maintenance of normal blood glucose levels in newborn depends on adequate glycogen stores,

maturation of pathways of glycogenolysis and gluconeogenesis and adequate endocrine response.

During immediate neonatal period after birth, the hormonal and metabolic adaptations ensure an adequate energy substrate for the vital organs in healthy full-term neonates, this hormonal-metabolic adaptation after birth fails to a variable extent in both preterm and small-for-gestational-age (SGA) infants. Therefore, hypoglycemia is more common in first seventy-two hours of life.

Overall incidence of neonatal hypoglycemia is 1 to 5 per 1,000 live births and in high risk neonates, it is up to 30% and differs in various parts of the world. In preterm and intrauterine growth retarded neonates, the incidence is 15% and 8% in large-for-gestational-age infants particularly in infants of diabetic mothers.¹ Neonatal hypoglycemia may be symptomatic and asymptomatic. Hypoglycemic neonates commonly present with refusal to feed, apathy jitteriness, convulsions, hypothermia, cyanosis and respiratory abnormality. After clinical evaluation hypoglycemia should always be confirmed by blood glucose estimation and response to treatment. Undiagnosed hypoglycemia can have long term neurological consequences; thus, the emphasis is on prevention and early detection along with treatment of asymptomatic hypoglycemia.²⁻⁴

Due to lack of significant correlation among plasma glucose concentration, clinical symptoms and long-term sequelae, definition of hypoglycemia in the newborn infant has remained controversial. Currently, the operational threshold for hypoglycemia is blood glucose value of < 40 mg/dl or plasma glucose < 45 mg/dl, in symptomatic newborn with plasma glucose < 45 mg/dl clinical interventions are indicated to increase blood glucose levels and in asymptomatic neonate with plasma glucose < 36 mg/dl surveillance of glucose levels should be done and intervention is required if symptoms appear or level do not increase after feeding.^{5,6}

Even after many years of research and debate there is limited evidence-based consensus regarding screening and management of neonates at risk of hypoglycemia, the dilemma exists.

Due to paucity of studies on neonatal hypoglycemia in rural hospital setup in the region this study was undertaken to know the incidence of hypoglycemia in high risk neonates to study etiology, risk factors, clinical presentation, screen blood glucose levels up to 72 hours after birth, and to study response to treatment and short-term outcome of these neonates.

Hypoglycemia is common in high risk neonates, screening of blood glucose levels along with clinical monitoring is important in diagnosis and proper management of these infants to reduce morbidity and mortality.

METHODS

This study was a Prospective observational Study that was conducted in Department of Paediatrics, AVBRH, Sawangi (Meghe), Wardha from period of 1st Aug 2016 to 31st July 2018. All neonates admitted in NICU with blood glucose levels less than 40 mg/dl at time of admission were included in present study after obtaining the informed consent. Neonates whose parents denied giving consent excluded from the study. All the details about the neonates included in the study were entered

along with detailed history, gestational age, birth weight, maternal risk factors, clinical examination finding, sequential blood glucose level at admission, 1 hour after feed/bolus, 6-hour, 12-hour, 24 hour, 48 hour and 72 hour of life along with management given and outcome. Statistical analysis was done by using inferential statistics, student t-test, chi-square test by using SPSS 22.0 software for data analysis.

Firstly, prick the heel for capillary blood with proper aseptic measure and screen the blood glucose level using reagent strip and glucometer in all neonates admitted in NICU. After pricking the heel, when blood comes out from the site of pricking collected drop of blood is touched the edge of test strip (white part of strip). After applying the drop of blood, white part of strip should not be visible. Blood will be drawn into the strip automatically. Test result will be appearing within 5 seconds.

RESULTS

Total number of deliveries were 4758 during study period out of which 889 neonates were admitted in NICU in which 200 had episode of hypoglycemia at the time of admission. Out of 200 hypoglycemic neonates, 47 had repeated episode of hypoglycemia after feeding or IV D10 bolus.

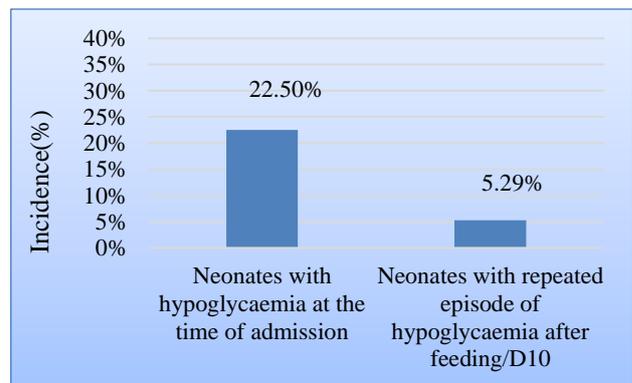


Figure 1: Incidence of hypoglycemia in high risk neonates.

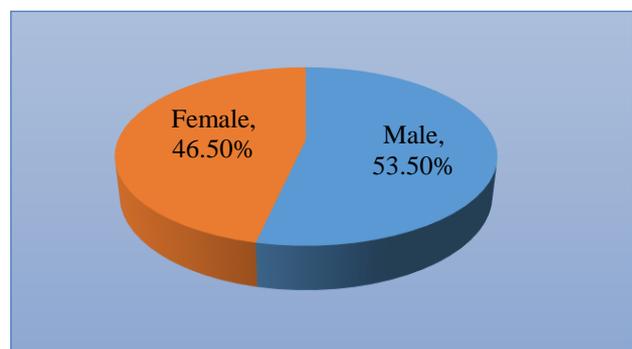


Figure 2: Sex distribution of all hypoglycemic neonates.

Incidence of hypoglycemia in high risk neonates was 22.49 % at time of admission during study period and incidence of two or more hypoglycemia episode in high risk neonates was 5.29 % (Figure 1).

Out of 200 hypoglycemic neonates, 53.5% males and 46.5% females and M: F ratio was 1.15:1 (Figure 2). 153 neonates suffered from single episode of hypoglycemia

which included 62(40.5%) pre-term and 91(59.5%) full term whereas in neonates who had more than one episode of hypoglycemia (n=47), there were 30(63.8%) pre-term and 17(36.2%) were full term. More than one episode of hypoglycemia was more common in Pre-term neonates whereas only single episode of hypoglycemia was more common in full term babies. This result was statistically significant (p=0.005, S).

Table 1: Risk factors of single episode and more than one episode of hypoglycemia.

| Variables | Single episode at admission (n=153) | | More than one episode (n=47) | | χ ² -value/p-value |
|------------------------------------|-------------------------------------|------|------------------------------|-------|-------------------------------|
| | FREQ. | % | FREQ. | % | |
| Gestational age | | | | | |
| Preterm | 62 | 40.5 | 30 | 63.8 | 7.86, p = 0.005, S |
| Term | 91 | 59.5 | 17 | 36.2 | |
| Post term | 00 | 00 | 00 | 00 | |
| Birth weight | | | | | |
| Macrosomia | 04 | 2.6 | 00 | 00 | 7.75, p = 0.020, S |
| NBW | 51 | 33.3 | 07 | 14.9 | |
| LBW | 98 | 64.1 | 40 | 85.1 | |
| Birth weight classification | | | | | |
| SGA | 29 | 19 | 18 | 38.3 | 6.29, p = 0.012, S |
| AGA | 115 | 75.1 | 29 | 61.7 | |
| LGA | 09 | 5.9 | 00 | 00 | |
| Maternal factor | | | | | |
| GDM | 13 | 8.5 | 8 | 17.02 | 1.92, p = 0.38, NS |
| Pre-eclampsia | 15 | 9.8 | 7 | 14.89 | |
| Prom | 14 | 9.2 | 3 | 6.38 | |
| Neonatal factor | | | | | |
| Birth asphyxia | 28 | 18.3 | 14 | 29.8 | 3.94, p = 0.046, S |
| RDS | 25 | 16.3 | 6 | 12.8 | 0.36, p = 0.54, NS |
| Early septicemia | 13 | 8.5 | 22 | 46.8 | 0.36, p = 0.54, NS |
| MSL | 20 | 13.1 | 3 | 6.4 | 2.85, p = 0.09, NS |

On comparing birth weight between neonates who suffered from single episode of hypoglycemia (n=153), LBW were 98(64.1%), NBW were 51(33.3%) and macrosomia were 4(2.6%) and in neonates who had more than one episode of hypoglycemia (n=47), LBW were 40(85.1%) and NBW 07(14.9%). LBW had prone for more than one episode of hypoglycemia which was statistically significant (p=0.020, S).

Comparison based on the classification of birth weight as SGA, AGA and LGA were 29(19%), 115(75.1%) and 09(5.9%) in single episode and SGA, AGA and LGA were 18(38.3%), 29(61.7%) and no LGA babies in more than single episode. SGA had more chances of hypoglycemia in more than single episode and revealed a statistically significant (p=0.012, S) result. When neonates (n=153) who suffered from single episode of hypoglycemia having maternal history of GDM 13(8.5%), pre-eclampsia 15(9.8%) and PROM 14(9.2%) were compared to neonates (n=47) who had more than

one episode of hypoglycemia having maternal history of GDM 8(17.02%), pre-eclampsia 7(14.89%) and PROM 3(6.38%). In neonates with more than one episode of hypoglycemic group, more mother had GDM and Preeclampsia when compared with single episode of admission group, but these factors were not statistically significant (p=0.38, NS).

Out of 153 neonates, birth asphyxia was seen in 28 (18.3%), early septicaemia in 13 (8.5%), RDS in 25 (16.3%) and MSL seen in 20 (13.1%). Out of 47 neonates, birth asphyxia was seen in 14 (29.8%), early septicaemia in 22 (46.8%), RDS in 6 (12.8%) and MSL in 3 (6.4%). Early septicaemia (p=0.0001, S) and birth asphyxia (p=0.046, S) were more common in 47 neonates who had suffered from more than one episode of hypoglycemia which was statistically highly significant (Table 1). Pre-term neonates were 62 in single episode of hypoglycemia group (n=153) in which pre-term (SGA) were 09(5.9%), pre-term (AGA) were 49(32.03%) and

pre-term (LGA) were 4(2.6%) whereas pre-term neonates were 30 in more than one episode of hypoglycemia group in which pre-term (SGA) were 12(25.5%), pre-term (AGA) were 18(38.3%) and no pre-term (LGA). Pre-term (SGA) commonly had more than one episode of hypoglycemia which was statistically highly significant (p=0.0002, S) whereas pre-term (AGA) (p=0.37, NS) and pre-term (LGA) (p=0.08, NS) were not statistically significant. In single episode of hypoglycemic group

(n=153), 91 were term neonates in which term (SGA) were 20(13.07%), term (AGA) were 66(43.1%) and term (LGA) were 5(3.3%) whereas in more than one episode of hypoglycemic group (n=47), 17 were term neonates in which term (SGA) were 06(12.08%), term (AGA) were 11(23.4%) and no term (LGA) babies seen. Term (AGA) was more in single episode of hypoglycemia and it is statistically significant (p=0.002, S) (Table 2).

Table 2: Correlation of gestational age and birth weight classification between neonates with single episode at admission and more than one episode of hypoglycemia (n=153 and 47).

| Variables | Pre-term | | | | χ^2 value / p-value | Term | | | | χ^2 value / p-value |
|-----------|----------|-------|--------|------|--------------------------|---------|-------|--------|------|--------------------------|
| | n=153 | | n = 47 | | | n = 153 | | n = 47 | | |
| | FREQ | % | FREQ | % | | FREQ | % | FREQ | % | |
| SGA | 09 | 5.9 | 12 | 25.5 | 13.78 p = 0.0002, S | 20 | 13.07 | 06 | 12.8 | Not calculated |
| AGA | 49 | 32.03 | 18 | 38.3 | 0.79 p = 0.37, NS | 66 | 43.1 | 11 | 23.4 | 9.04 p = 0.002, S |
| LGA | 04 | 2.6 | 00 | 00 | 3.04 p = 0.08, NS | 05 | 3.3 | 00 | 00 | 3.04 p = 0.08, NS |

In neonates with single episode of hypoglycemic group (n=153) presented with poor feeding 31(20.3%), lethargy 32(20.9%), jitteriness 31(20.3%), seizure 22(14.4%), respiratory abnormality 59(38.6%) and 93(60.8%) had no symptoms. In neonates with more than one episode of hypoglycemic group (n=47) presented with poor feeding 40(85.1%), lethargy 40(85.1%), jitteriness 13(27.7%), seizure 29(61.7%), respiratory abnormality 25(53.2%) and 3(6.4%) were asymptomatic. Most common symptoms in more than single episode of hypoglycemic group (n=47) were poor feeding, lethargy, seizure and respiratory abnormality and these symptoms were highly statistically significant (p=0.0001, S) whereas jitteriness as symptom was not statistically significant (p=0.18, NS). Asymptomatic neonates were more in single episode of hypoglycemic group (n=153) which was statistically highly significant (p=0.0001, S) (Figure 3).

Out of 153 neonates, 131(85.6%) had blood glucose level between 31-39 mg/dl, 29 (13.1%) between 25-30 mg/dl and 2(1.3%) were below 25 mg/dl compared with out of 47 neonates who had 30(63.8%), 12(25.5%) and 5(10.7%) neonates with blood glucose level between 31-39 mg/dl, 25-30 mg/dl and below 25 mg/dl respectively.

The blood glucose levels at admission were in lower range (less than 30 mg/dl) in 47 neonates who later had repeat episode of hypoglycemia, this result was statistically significant (p=0.0007,S) whereas blood glucose level more than 30 mg/dl were more common in single episode of hypoglycemic group (n=153), this too was statistically significant (p=0.0007,S) (Table 3).

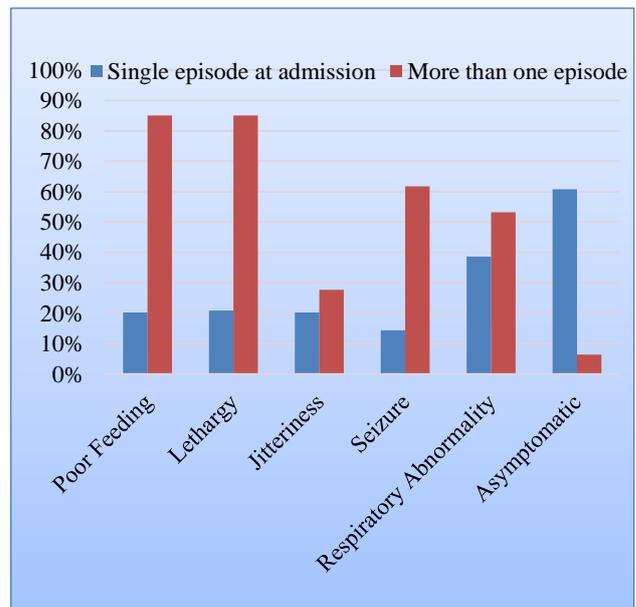


Figure 3: Correlation of clinical feature between single episode and more than one episode of hypoglycemic neonates.

Out of 47 neonates who had more than one episode of hypoglycemia, total number of hypoglycemic episodes were 80 in which after one hour after IV bolus or feed, 9 (11.25%) episodes of hypoglycemia were seen. At 6 hours 21 (26.25%) episodes, 27 (33.75%) episodes at 12 hours, 12 (15%) episodes at 24 hours, 8 (10%) episodes at 48 hours, 3 (3.75%) episode at 72 hours of life.

Maximum number of hypoglycemic episodes were 57(71.25%) within 24 hours of life than 20(25%) episode at 24-48 hours of life and less hypoglycemic episode at 48-72 hours of life. It shows that risk of hypoglycemia was maximum 27(33.75%) at 12 hours of life. (Figure 4)

Mean blood glucose at particular time of 0-2 hour, after 1 hour of giving IV bolus or feed, 6hour, 12-hour, 24-hour, 48 hour and 72 hour. At the time of admission, 34.68 were mean blood glucose level. 35.44, 33.67, 34.56, 36.17, 35.63 and 35 were mean blood glucose level at after 1 hour of giving IV bolus or feed, 6hour, 12-hour,

24-hour, 48 hour and 72 hour respectively. Mean blood glucose level was lower (34.56) at 12 hours of life and lowest (33.67%) at 6 hours of life (Figure 5).

The total number of hypoglycemia episodes experienced by the neonates up to the first 72 hours of life. Out of a total of 47 neonates, 25 neonates (53.2%) experienced 1 episode of hypoglycemia, while 13 neonates (27.7%) experienced 2 episodes of hypoglycemia. The remaining 9 neonates (19.1%) experienced 3 or more episodes of hypoglycemia (Table 4).

Table 3: Correlation of blood glucose level at the time of admission between neonates with single episode at admission and more than one episode of hypoglycemia (n=153 and 47).

| Blood glucose level | Single Episode at admission (n=153) | | More than one episode (n=47) | | χ ² -value/p-value |
|---------------------|-------------------------------------|------|------------------------------|------|-------------------------------|
| | FREQ | % | FREQ | % | |
| 31 – 39 | 131 | 85.6 | 30 | 63.8 | 14.55,p=0.0007,S |
| 25 – 30 | 20 | 13.1 | 12 | 25.5 | |
| < 25 | 02 | 1.3 | 05 | 10.7 | 14.55,p=0.0007,S |



Figure 4: Percentage of hypoglycemic episode during screening after admission.

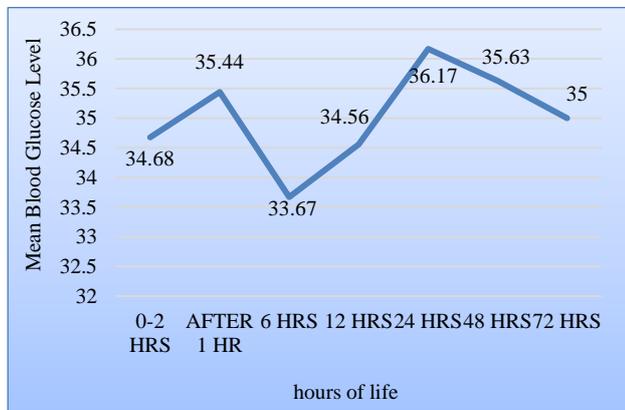


Figure 5: Mean hypoglycemic blood glucose level during screening period.

Table 4: Analysis of each neonate with number of hypoglycemia episode (n=47).

| Episodes of hypoglycemia | No. of neonates | % |
|--------------------------|-----------------|------|
| 1 | 25 | 53.2 |
| 2 | 13 | 27.7 |
| ≥3 | 09 | 19.1 |

Out of 153 neonates experiencing a single episode of hypoglycemia, 66 neonates (43.1%) were treated with oral feeds, 87 neonates (56.9%) were treated with bolus of 10% dextrose and none of the neonates required glucose infusion drip.

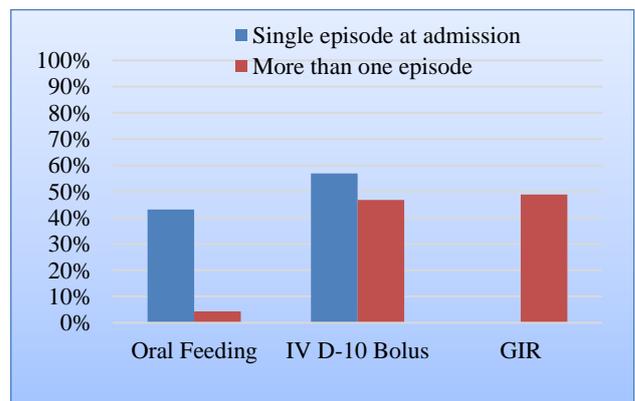


Figure 6: Correlation of management between single episode and more than one episode of hypoglycemic neonates.

Out of 47 neonates who experienced more than 1 episode of hypoglycemia, 2 neonates (4.3%) were treated with

oral feeds, 22 neonates (46.8%) were treated with bolus of 10% dextrose and 23 neonates (48.9%) were started on glucose infusion drip. Oral feeding was effective in single episode of hypoglycemia group and this finding was statistically significant ($p=0.0001$, S). Glucose infusion drip was effective in more than one episode of hypoglycemia group and this finding was statistically significant ($p=0.0001$, S) (Figure 6).

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. Out of 47 neonates with more than 1 episode of hypoglycemia, 40 neonates (85.1%) were discharged while the other 7 neonates (14.9%) died.

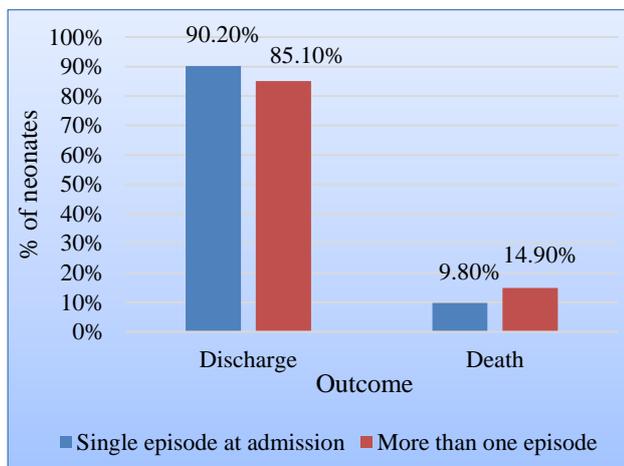


Figure 7: Correlation of outcome between single episode and more than one episode of hypoglycemic neonates.

Mortality was slightly higher in more than one episode of hypoglycemia group ($n=47$) but it was not statistically significant ($p=0.28$, NS) (Figure 7).

DISCUSSION

In the present study, total number of live births during the study period were 4758 out of them 889 (18.63%) neonates were admitted in NICU in which 200 had episode of hypoglycemia at the time of admission. Out of 200 hypoglycemic neonates, 47 had repeat episode of hypoglycemia after feeding or IV D10 bolus.

Incidence of hypoglycemia in high risk neonates was 22.49 % at time of admission and incidence of two or more hypoglycemia episode in them was 5.29 %. The incidence of hypoglycemia in high risk neonates admitted to NICU as found in present study, was slightly similar to the incidence rates of the studies carried out by Hosagasi NH et al and Singh YP et al.^{7,8}

Overall M: F ratio in current study was 1.15:1 which is similar to studies by Rasmussen et al and Saifuddin AA et al and slightly similar to studies by De AK et al,

Dhananjaya CP et al, Manjunatha BR et al and Singh YP et al.^{9,10,5,11,12,8}

The ratio of pre-term, term and post-term neonates at risk of hypoglycemia in the current study was similar to those found in the studies by Manjunatha et al, Indira et al, Burdan et al and Bhand et al.¹²⁻¹⁵ The ratio of pre-term, term and post-term neonates did not match with studies by Singh YP et al and De AK et al in which pre-term neonates are less whereas in study by Dhananjaya CP et al post-term neonates were 10.5%.^{8,5,11}

In the current study, we found that higher chances of hypoglycemia episode were present in low birth weight babies and similar to studies done by De AK et al and Indira P et al.^{5,13}

AGA babies had more chances of hypoglycemia in current study could be because of more number of AGA babies admitted in NICU during study period which is similar to study done by Singh YP et al.⁸

In current study most, neonates with hypoglycemia had maternal risk factors such pre-eclampsia, GDM and PROM for neonatal hypoglycemia. GDM was also a common maternal risk factor in studies done by Manjunatha BR et al, Singh YP et al and Bhand SA et al which is similar to the current study.^{8,12,15} Pre-eclampsia was also present in Amarendra M, Manjunatha BR et al, Singh YP et al and Bhand SA et al which is similar to the current study.^{16,12,15,8} PROM as maternal risk factor was only present in Amarendra M et al study which is similar to current study.

In current study birth asphyxia was more common neonatal risk factor than early septicaemia and RDS which was similar to study done by Dhananjaya CP et al, Burden et al and Manjunatha BR et al.^{11,14,12} Early septicemia was more common in the study done by Indira P et al and Stomnaroska et al and RDS was more common in the study by Bhand SA et al so that these are not similar to current study.^{13,17,16}

Most common symptoms of hypoglycemia were poor feeding, lethargy, jitteriness, seizure and respiratory abnormality which was similar to study done by Dhananjaya CP et al, Indira P et al, Amarendra N et al, Dashti N et al, Manjunatha BR et al, Singh YP et al, Saifuddin AA et al and Bhand SA et al.^{11,13,16,18,12,8,10,15}

In the current study, blood glucose level below 30 mg/dl was more commonly seen in neonates having more than one episode of hypoglycemia. The blood glucose levels at admission were in lower range in neonates who later had repeat episode of hypoglycemia. This correlation of blood sugar level at admission and repeat episode of hypoglycemia has not been discussed in other studies.

Most of hypoglycemic episode were occur within 24 hours of life or on 1st day in current study and similar to

most of studies done by Indira P et al, Amarendra N et al, Singh YP et al, Saifuddin AA et al and Saini A et al.^{13,16,8,10,19}

Most of hypoglycemic neonates had experienced only one episode in repeat episode of hypoglycemic group in current study which is similar to study done by Amarendra et al.¹⁶

In the current study, oral feeding or intravenous dextrose bolus was effective in single episode of hypoglycemia and intravenous D10 bolus or glucose infusion drip was effective in more than one episode. Intravenous D10 bolus was equally effective in both single episode and more than one episode of hypoglycemia.

This mortality rate is higher in Najati N et al study as compared to current study and this difference could be because in their study preterm neonates were more than current study.²⁰

CONCLUSION

Preterm, LBW, SGA, GDM, pre-eclampsia, birth asphyxia and early septicaemia and hypothermia are at an increased risk of developing hypoglycemia in the current study. Most frequent manifestations of hypoglycemia were poor feeding, lethargy, seizure and respiratory abnormality. The blood glucose levels at admission were less than 30 mg/dl in neonates who later had repeat episode of hypoglycemia and higher number of hypoglycemia episode after admission occurred within 24 hours of life during screening period. Repeated episode of hypoglycemia had slightly increased chances of mortality in neonates. Neonates with hypoglycemia should be diagnosed and managed timely according to protocol to reduce neonatal mortality.

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

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