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Original Research Article

Study of Hypoglycemia in At Risk Neonates and their Neurodevelopmental Outcome

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Abstract:

Introduction: Hypoglycemia amongst neonates is the most commonly encountered metabolic problem and is known to be due to failure of metabolic adaptation to the postnatal environment. Premature, small for gestational age, neonates born to mother with insulin dependent diabetes mellitus or gestational diabetes, and neonates with hyperinsulinaemia are at high risk for developing neonatal hypoglycemia.[9,10] The rate of hypoglycemia amongst neonates born to diabetic mothers ranges between 8–30% whereas that amongst neonates of non-diabetic mother is much lower i.e. approximately 3%.

Objectives: To determine incidence of hypoglycemia and factors associated with hypoglycemia in at risk neonates

Methodology: This study was conducted among sick newborn care unit, Department of Pediatrics, Gandhi Medical College and associated Kamla Nehru Hospital, Bhopal from 1st October 2018 to 31st March 2020. All the at risk neonates diagnosed as hypoglycemia (Blood glucose ≤45 mg/dl) in SNCU i.e. small for gestational age, low birth weight babies, large for gestational age and infant of diabetic mother were includes for this study. Neonates admitted in SNCU with Moderate to severe Respiratory distress, Perinatal asphyxia, Shock, Sepsis, Congenital heart diseases, Major congenital Malformation & Meconium aspiration syndrome were excluded from the study.

Results: Majority of neonates in both the groups (96.7%) belonged to age range of less than or equal to 6 hours whereas only 3.3% neonates were aged more than 6 hours. Mean age of neonates with and without hypoglycaemia was 3.28±1.55 and 3.04±1.52 hours respectively. In present study, out of 50 hypoglycaemic neonates, 40% were males whereas 60% were females. Similarly out of 70 neonates with normal RBS levels, 44.3% were males whereas 55.7% were females. About 76% neonates with hypoglycaemia were inborn whereas 24% were outborn. Similarly, about 82.9% neonates with normal glycaemic status were inborn whereas only 17.1% neonates were outborn.

Conclusion: Our study conclude that Pre-eclampsia was significantly associated with neonatal hypoglycaemia. Common risk factors among neonates with hypoglycaemia were low birth weight, NNH, and IUGR but no statistically significant association between these factors and hypoglycaemia was observed. Hypoglycaemia significantly affect neurodevelopmental outcome of neonates in long term.

Keywords: Hypoglycemia, Neonates, Risk Factors, Neurodevelopmental Outcome.

Introduction

Hypoglycemia amongst neonates is the most commonly encountered metabolic problem and is known to be due to failure of metabolic adaptation to the postnatal environment.[1] Immediately following birth, there is a shift from maternal environment to external environment and the continuous supply of glucose which was initially being provided through placenta is interrupted; thus successful transition to neonatal life requires adequate fuel stores, mature glycogenolytic and gluconeogenic pathways and hormonal homeostatic systems.[2,3] The exact definition of hypoglycemia is still debatable with no universally accepted safe blood glucose concentration for newborns,[4,5,6] however, the guidelines issued by American Academy of Pediatrics recommends treatment of hypoglycemia at blood glucose level of <45 mg/dl.[7] Whereas, the Pediatric Endocrine Society recommends that in babies at risk of hypoglycaemia, glucose concentrations should be

maintained >50 mg/dL.[8] Premature, small for gestational age, neonates born to mother with insulin dependent diabetes mellitus or gestational diabetes, and neonates with hyperinsulinaemia are at high risk for developing neonatal hypoglycemia.[9,10]

The rate of hypoglycemia amongst neonates born to diabetic mothers ranges between 8–30% whereas that amongst neonates of non-diabetic mother is much lower i.e. approximately 3%.[11] Since the incidence of gestational diabetes are increasing due to life style changes, incidence of neonatal hypoglycemia are also on rise.[12] It has been documented by various studies that asymptomatic infants with transient hypoglycemia are at very low risk of neurologic complications,[13,14] however, prolonged and recurrent episodes of hypoglycemia are often associated with acute systemic effects and neurological sequelae.[15] Pathogenesis which may lead to brain injury during hypoglycemia could be attributed to hypersensitivity of neuron and glial cells to low glucose level as glucose is an essential molecule that supplies energy for brain consumption.[16,17] Blood glucose monitoring preferably within 72 hours after birth is useful for the prevention as well as treatment of neonatal hypoglycemia and associated brain injury. The neonate may present with nonspecific neurological symptoms such as irritability, seizures, hypotonia, exaggerated moro reflex, lethargy, tremor, jitteriness and acute encephalopathy. Neurological events due to resultant hypoglycemia may manifest as cerebral palsy, mental retardation, microcephaly, refractory epilepsy, ataxia, learning cognitive disability and loss of vision. In severe cases, this may even lead to hypoxic-ischemic injury [18,19] While most hypoglycemic newborns do not develop neurologic sequelae, a few will have some degree of neurological impairment. The present study was thus undertaken with the broad objective to assess the incidence of hypoglycemia among at risk neonates presenting with varying clinical manifestations and to study their neurodevelopmental outcomes.

Objectives: To determine incidence of hypoglycemia and factors associated with hypoglycemia in at risk neonates

Material and Methods:

This Prospective observational cohort study was conducted in Sick newborn care unit, Department of Pediatrics, Gandhi Medical College and associated Kamla Nehru Hospital, Bhopal from 1st October 2018 to 31st March 2020. All the at risk neonates diagnosed as hypoglycemia (Blood glucose ≤45 mg/dl) in SNCU i.e. small for gestational age, low birth weight babies, large for gestational age and infant of diabetic mother were includes for this study. Neonates admitted in SNCU with Moderate to severe Respiratory distress, perinatal asphyxia, Shock, Sepsis, Congenital heart diseases, Major congenital Malformation & Meconium aspiration syndrome were excluded from the study. All the patients fulfilling the inclusion criteria were selected using purposive sampling. Written consent was obtained from the parents/guardians of all the neonates after explaining them the nature and purpose of the study. They were assured that confidentiality would be strictly maintained. The option to withdraw from the study was always open.

Methodology:

After obtaining ethical clearance from Institute's ethical committee, written consent was obtained from parents/guardian of neonates. All at risk neonates with hypoglycemia satisfying the inclusion criteria i.e. small for gestational age, low birth weight babies, large for gestational age and infant of diabetic mother admitted in SNCU at our institution were enrolled during the study period. Details regarding sociodemographic profile of parents was obtained and entered in questionnaire. Also mothers were enquired about antenatal visits, Last menstrual period, perinatal period, maternal diseases and recorded in the pretested proforma. Details regarding mode of delivery, indication of LSCS in case of cesarean delivery, and birth weight along with anthropometry including weight, length and head circumference were recorded in questionnaire. Vitals at the time of admission were also noted. Gestation was assessed using New Ballard score. Random blood glucose was estimated by glucometer (accucheck) at 2nd, 6th, 12th, 24th and 48th hours of birth under aseptic precautions and those babies in whom hypoglycemia was detected were managed as per protocol. Neurodevelopmental assessment was done by two methods at 3, 6, 9 and 12 months of age

1. Screening by Trivendram Development Screening Chart (TDSC) and
2. Confirmatory by Development Assessment Scales for Indian Infants (DASII)

Data was compiled using MS Excel and analysed using SPSS version 20.0 for Windows (IBM Corporation Armonk, NY, and USA. Frequency and percentage was calculated & appropriate statistical test was applied wherever applicable; $P<0.05$ was considered as statically significant.

Observation and results:

Table 1: Distribution according to hypoglycemia

Hypoglycemia	Present	Absent
N (%)	50 (41.7)	70 (58.3)
Mean ± SD	33.22±6.31	58.14±8.89
95% CI	31.43-35.01	56.02-60.26

Mean RBS among 120 neonates was 47.76±14.64 mg/dl (95% CI- 45.11- 50.41). Out of 120 neonates, hypoglycemia (<45 mg/dl) was documented in 50 (41.7%) neonates. The mean RBS in hypoglycemic neonates was 33.22±6.31 mg/dl (95% CI- 31.43-35.01) whereas mean RBS among 70 normoglycemic neonates was 58.14±8.89 mg/dl (95% CI- 56.02-60.26).

Table 2: Association between age and glycemic status of neonates

Age (hours)	Hypoglycemia				Total (n=120)	
	Present (n=50)		Absent (n=70)			
	n	%	n	%	n	%
≤6	48	96	68	97.1	116	96.7
>6	2	4	2	2.9	4	3.3
Mean±SD	3.28±1.55		3.04±1.52		3.14±1.53	
95% CI	2.84-3.72		2.68-3.40		2.87-3.42	
$\chi 2$	0.118					
P value	0.73					

Majority of neonates in both the groups (96.7%) belonged to age range of less than or equal to 6 hours whereas only 3.3% neonates were aged more than 6 hours. Mean age of neonates with and without hypoglycaemia was 3.28±1.55 and 3.04±1.52 hours respectively. Test of significance (chi square test) showed no statistically significant association between age and glycemic status among at risk neonates (p>0.05).

Table 3: Association of maternal risk factors with glycaemic status of neonates

Maternal Risk factors	Hypoglycemia				Total (n=120)		$\chi 2$	P value
	Present (n=50)		Absent (n=70)					
	n	%	n	%	n	%		
Preeclampsia	11	22	5	7.1	16	13.3	5.57	0.02
Anemia	7	14	8	11.4	15	12.5	0.17	0.67
APH	4	8	9	12.9	13	10.8	0.71	0.39
Twin	5	10	3	4.3	8	6.7	1.5	0.22
Oligo	2	4	4	5.7	6	5	0.18	0.67
Eclampsia	2	4	3	4.3	5	4.2	0.01	0.94
GDM	4	8	1	1.4	5	4.2	3.15	0.08
PROM	1	2	3	4.3	4	3.3	0.47	0.49
PIH	0	0	2	2.9	2	1.7	0.23	0.63
Placenta previa	0	0	1	1.4	1	0.8	0.72	0.39
Heart dis	0	0	1	1.4	1	0.8	0.72	0.39
IUGR	0	0	1	1.4	1	0.8	0.72	0.39
Prolonged labor	0	0	1	1.4	1	0.8	0.72	0.39
PPH	1	2	0	0	1	0.8	0.73	0.86
No risk	13	26	28	40	41	34.2	2.54	0.11

Most common maternal risk factor for hypoglycaemia was preeclampsia observed in 22% neonates, followed by anemia (14%) and twin delivery. In present study, pre-eclampsia was observed to be significantly associated with neonatal hypoglycaemia among maternal risk factors (p<0.05) whereas no other maternal risk factor was associated with neonatal hypoglycaemia (p>0.05).

Table 4: Association of glycaemic status with neonatal risk factors

Neonatal risk factors	Hypoglycemia				Total (n=120)		$\chi 2$	P value
	Present (n=50)		Absent (n=70)					
	n	%	n	%	n	%		
LBW	29	58	35	50	64	53.3	0.75	0.39
NNH	3	6	10	14.3	13	10.8	2.07	0.15
IUGR	3	6	8	11.4	11	9.2	1.03	0.31
HIE	1	2	2	2.9	3	2.5	0.47	0.49
NEC	2	4	1	1.4	3	2.5	0.79	0.37

NNH/sepsis	0	0	1	1.4	1	0.8	0.72	0.39
NNH/NEC	0	0	1	1.4	1	0.8	0.72	0.39
RDS	0	0	1	1.4	1	0.8	0.72	0.39
No risk	12	24	11	15.7	23	19.2	1.39	0.25

Most common risk factor among neonates with hypoglycaemia was low birth weight (58%), followed by NNH and IUGR in 6% neonates each. In present study, no statistically significant association of glycaemic status was observed with various risk factors (p>0.05).

Table 5: Assessment of development using Trivandrum Developmental Screening Chart (TDSC)

Timing	TDSC	Hypoglycemia				Total (n=120)		χ2	P value
		Present (n=50)		Absent (n=70)					
		N	%	n	%	n	%		
3 months	Normal	31	62	57	81.4	88	73.3	6.33	0.04
	Delay	18	36	13	18.6	31	25.8		
	Died	1	2	0	0	1	0.8		
6 months	Normal	34	68	61	87.1	95	79.2	7.04	0.03
	Delay	15	30	9	12.9	24	20		
	Died	1	2	0	0	1	0.8		
9 months	Normal	34	68	63	90	97	80.8	9.5	0.009
	Delay	15	30	7	10	22	18.3		
	Died	1	2	0	0	1	0.8		
12 months	Normal	34	68	63	90	97	80.8	9.5	0.009
	Delay	15	30	7	10	22	18.3		
	Died	1	2	0	0	1	0.8		

Mortality was observed in 1 neonate in hypoglycaemia group and none in normoglycemia group. Among hypoglycemic neonates, development delay was noted in 36% neonates at 3 months and 30% at 6, 9 and 12 months each. However, among neonates with normal glycemic status, development delay was observed in 18.6% at 3 months, 12.9% at 6 months and 10% neonates at 9 and 12 months each. The present study observed statistically significantly higher developmental delay in hypoglycaemic neonates as compared to normoglycaemic neonates at all follow up (p<0.05).

Table 6: Association between DQ (using DASII) and hypoglycaemia

DQ		Hypoglycemia				Total (n=119)		χ2	P value
		Present (n=49)		Absent (n=70)					
		n	%	n	%	n	%		
Cumulative DQ	>70	43	87.8	68	97.1	111	93.3	4.35	0.114
	70-60	5	10.2	2	2.9	7	5.9		
	50-60	1	2	0	0	1	0.8		
Motor DQ	>70	43	87.8	68	97.1	111	93.3	4.74	0.09
	70-60	5	10.2	1	1.4	6	5		
	50-60	1	2	1	1.4	2	1.7		
Mental DQ	>70	34	69.4	63	90	97	81.5	8.13	0.017
	70-60	11	22.4	5	7.1	16	13.4		
	50-60	4	8.2	2	2.9	6	5		

In present study, cumulative DQ and motor DQ was >70 in 87.8% and 97.1% neonates with hypoglycaemia and normoglycemia respectively. In about 10.2% neonates with hypoglycaemia, cumulative DQ ranged between 60 -70. However, no statistically significant association was observed of cumulative and motor DQ with glycaemic status (p>0.05). Mental DQ was significantly lower in neonates with hypoglycaemia i.e. it was less than 70 in 30.6% as compared to 10% neonates with normolycemia (p<0.05).

Table 7: Association of hypoglycmia with Motor DQ

Motor DQ		Hypoglycemia				Total (n=119)		χ2	P value
		Present (n=49)		Absent (n=70)					
		n	%	n	%	n	%		
Neck	90	31	63.3	61	87.1	92	77.3	10.4	0.006
	75	16	32.7	9	12.9	25	21		
	50	2	4.1	0	0	2	1.7		
Body	90	27	55.1	38	54.3	65	54.6	13.6	0.001
	75	14	28.6	32	45.7	46	38.7		
	50	8	16.3	0	0	8	6.7		
Locomotion I	90	11	22.4	25	35.7	36	30.3	2.98	0.39
	75	25	51	30	42.9	55	46.2		
	50	11	22.4	14	20	25	21		
	25	2	4.1	1	1.4	3	2.5		
Locomotion II	90	10	20.4	8	11.4	18	15.1	3.39	0.335
	75	6	12.2	15	21.4	21	17.6		
	50	23	46.9	36	51.4	59	49.6		
	25	10	20.4	11	15.7	21	17.6		
Manipulation	90	24	49	42	60	66	55.5	3.77	0.29
	50-75	21	42.8	26	37.1	47	39.5		
	50	4	8.2	2	2.9	6	5		

Neck and body component of motor DQ was observed to be significantly low among neonates with hypoglycaemia as compared to neonates with normal glycaemic status ($p<0.01$). However, no such association was documented for locomotion I and II and manipulation component of motor DQ with glycaemic status ($p>0.05$).

Discussion

Hypoglycemia, one of the most common metabolic problems among neonates has been associated with morbidity as well as mortality among neonates. Apart from this, neonatal hypoglycemia has been associated with significantly higher risk of developmental delays among children of preschool age.[20] The present study was conducted on a total of 120 high risk neonates admitted in SNCU to determine incidence of hypoglycemia and factors associated with hypoglycemia in at risk neonates and to assess neurodevelopmental outcomes of hypoglycemic neonates. At risk neonates for development of hypoglycemia include premature, SGA, neonates of diabetic mother, or gestational diabetes etc.[9,10] The cut-off value of hypoglycemia in present study was 45 mg/dl. In present study, incidence of hypoglycemia was 41.7% among at risk neonates. Mean RBS levels among hypoglycemic and normoglycemic neonates were 33.22±6.31 mg/dl and 58.14±8.89 mg/dl respectively. The incidence of hypoglycemia in a study by Mitchell NA et al (2020) was 33.7% which was lower as compared to present study.[21]

However, Kumar TJ et al (2018) also documented lower incidence of hypoglycemia in their cross sectional study i.e. 33.3% as compared to present study.[22] The observed difference between present study and reference study could be due to difference in inclusion criteria. In present study high risk neonates were included and cut-off value for hypoglycemia was 45 mg/dl, whereas in reference study, cut-off values were 40 mg/dl. The incidence of hypoglycemia has been reported to be higher in males as compared to females.[23,24] In present study, hypoglycemia was observed in 40% males and 60% females, however, the observed association was statistically insignificant ($p>0.05$). The findings of present study were supported by findings of Yunarto Y et al (2019) in which out of 123 neonates with hypoglycemia, majority were females (64) and 59 were males.[25] Serum glucose levels begin to decline 1 to 3 hours after birth and may present with hypoglycaemia. This has been attributed to rapid transition of environment leading to hyperinsulinemia after birth when the supply of glucose from the placenta is interrupted.[26] Age in hours was calculated for all the neonates. In our study, majority of neonates with hypoglycaemia presented within 6 hours of birth with mean age of 3.28±1.55 hours. However the observed association of age with hypoglycemia was statistically insignificant ($p>0.05$).

These findings were supported by study of Begum S et al (2018) in which about 85% neonate of mothers with insulin dependent diabetes developed hypoglycemia within 6 hours of birth (P-value<0.01).[27] The association of maternal age and hypoglycaemia in neonates have not been established. In present study, no statistically significant association was observed between maternal age and hypoglycaemia ($p>0.05$). Van Howe RS et al (2006) in their study documented that mean blood glucose levels in neonates is lowest during the first 3 hours following birth and the risk of blood glucose level <30 mg/dl decrease

with increase in maternal age.[28] In present study, maternal haemoglobin was greater than 10 gm% in majority of neonates and mean haemoglobin levels in neonates with hypoglycaemia and normoglycemia was 10.44±1.09 gm/dl and 10.36±0.92 gm/dl respectively. The observed association was statistically insignificant ($p>0.05$) in our study. Bhagat B et al (2017) in their study concluded that maternal haemoglobin levels between 10 and 13 gm/dl are optimal for fetal growth as well as wellbeing. Hemoglobin at this level is associated with less incidence of neonatal complications.[29] Multiple risk factors have been associated with hypoglycemia. These factors include insulin dependent diabetes mellitus, maternal pre-eclampsia and eclampsia, oligohydramnios, gestational diabetes mellitus etc.[30] In present study, amongst various maternal factors, pre-eclampsia among mothers was significantly associated with hypoglycaemia in neonates ($p<0.05$). These findings were supported by findings of Mitchell NA et al (2020) in which maternal hypertension (OR 3.07, 95% CI 1.51–6.30, $p = 0.002$) was the sole risk factor for neonatal hypoglycemia.[21] Gestational age is an independent risk factors associated with hypoglycaemia. Among preterm neonates, glycogen stores are deficient usually, depending upon age at birth. Also perinatal asphyxia is common in preterm neonates which is also an important contributor of deficient glycogen stores.[26] In present study, majority of neonates with hypoglycaemia were preterm (885) as compared to 65.7% neonates with normoglycemia. The observed association of gestational age with hypoglycaemia was statistically highly significant ($p<0.01$).

These findings were consistent with findings of Yunarto Y et al (2019), where about 47.1% neonates who developed hypoglycaemia were preterm. Odds of occurrence of hypoglycemia was 6.54 times among preterm neonates as compared to term neonates ($P <0.001$).[25] Various risk factors such as birth asphyxia, low birth weight, Small for gestational age, large baby, Respiratory distress, Sepsis, inadequate feeding etc.[31] In present study, amongst various factors, common risk factors among hypoglycemic neonates were low birth weight (58%), followed by NNH and IUGR in 6% neonates each but the observed association was not statistically significant ($p>0.05$). Majority of neonates with hypoglycaemia and normoglycemia belonged to age range of 1.5 to 2 kg (58% and 68.7% respectively). About 12% neonates with hypoglycaemia had birth weight >3 kg whereas that in normoglycmic neonate was 1.4% and the association was borderline significant ($p=0.05$). The higher mean age among hypoglycemic neonates in present study could be due to macrosomic neonates born to diabetic mother which is a significant risk factor for hypoglycaemia. These findings were consistent with findings of Anjum R et al (2019) in which neonatal risk factors were hypothermia (22%), endocrine disorder (7%), low birth weight (48%), small for gestational age (29%), respiratory distress (31%) and sepsis (20%).[32] The clinical presentation of neonatal hypoglycemia are often nonspecific and in neonates hypoglycemia may manifest even without symptoms.

Neonate may with neurological symptoms like seizure, lethargy, hppotonia, jitteriness, poor feeding etc which are usually nonspecific.[33] In present study, statistically significantly higher occurrence of seizures, lethargy, poor feeding, and tachycardia was observed among hypoglycaemic neonates as compared to neonates with normal glycaemic levels ($p<0.05$). Our study findings were consistent with findings of Anjum R et al (2019). They documented hypothermia, jitteriness, lethargy and seizures in 39%, 34%, 32% and 9% neonates with hypoglycemia respectively.[32] Similar findings were documented by Singh YP et al (2014) in which most common symptom of hypoglycemia was jitteriness (88.9%) observed in 8 out of 9 symptomatic hypoglycemic cases.[34]

Conclusion

Based upon the findings of present study, it can be concluded that Pre-eclampsia was significantly associated with neonatal hypoglycaemia. Gestational age of neonate i.e. prematurity and hypoglycaemia was significantly associated. Common risk factors among neonates with hypoglycaemia were low birth weight, NNH, and IUGR but no statistically significant association between these factors and hypoglycaemia was observed. Neonatal birth weight and hypoglycaemia showed borderline association. Seizures and lethargy along with poor feeding, and tachycardia were significantly associated with hypoglycaemia. Hypoglycaemia significantly affect neurodevelopmental outcome of neonates in long term.

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