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Hypoglycemia in Neonates More than 1500 Gram Weight with No Secondary Cause – Its Effects and Outcome.

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ABSTRACT

Background: Aim: 1) To study the outcome of hypoglycemia in neonates weighing >1500gram both symptomatic and asymptomatic having exclusively hypoglycemia with no any other medical condition known to cause brain damage , till 9 months of corrected gestational age(CGA).2) To study the clinical profile of hypoglycemia in neonates weighing >1500gram. **Methods:** 35 neonates weighing >1500gram with hypoglycemia (<40 mg/dl), both symptomatic and asymptomatic without any other medical condition known to cause brain damage were enrolled in the study. Hypoglycemia was confirmed with venous sample laboratory value. Both neonatal and maternal history was taken in detail, clinical examination, anthropometry was done. Follow up was done at 3, 6, 9 months of CGA for assessing neurodevelopmental outcome (motor developmental quotient i.e. MoDQ and mental developmental quotient i.e. MeDQ using DASII6 i.e. development assessment scale for Indian infants) and we did anthropometry and clinical examination, ultrasonography at discharge, electroencephalogram (EEG) done in patients with seizure, Magnetic Resonance Imaging (MRI) at 3 months, Brainstem evoked response audiometry (BERA) at 6 months, vision assessment at 9 months of CGA. Appropriate statistical analysis was done to calculate results. **Results:** Out of 35 enrolled cases follow up was possible in 30 cases. In our study, the prevalence of abnormal neurodevelopmental outcome according to DASII6 was 53.33% (n=16) cases with abnormal MoDQ (<70%) and 56.66% (n=17) cases with abnormal MeDQ (<70%) at 3, 6, 9 months of CGA respectively. There was statistically significant difference in the mean values of MoDQ (p value 0.014, 0.011, 0.02) and mean MeDQ (p value 0.019, 0.008, 0.02) on follow up at 3, 6, 9 months of corrected gestational age respectively between symptomatic and asymptomatic hypoglycemic cases. 8 (57.14%) symptomatic cases and 6 (37.5%) asymptomatic cases had microcephaly on follow up and the difference was not statistically significant. MRI was abnormal in 10 (71.4%) symptomatic cases and 6 (37.5%) asymptomatic cases and the difference was not statistically significant. Ultrasonography was done in all cases at discharge and it was found abnormal in 2(5.7%) cases. BERA, vision assessment and EEG was normal in all cases. **Conclusion:** Both symptomatic and asymptomatic hypoglycemia leads to abnormal neurodevelopmental outcome but it is more poor in symptomatic neonates as compared to asymptomatic hypoglycemia.

Keywords: Neurodevelopmental; MoDQ; MeDQ; DASII; hypoglycemia; blood glucose.

INTRODUCTION

Hypoglycemia is historically one of the most common metabolic problems seen in both newborn nursery and NICU; but confirming a diagnosis of clinically significant hypoglycemia requires that one interpret the blood glucose values within the clinical context. The definition of hypoglycemia as well as its clinical significance, management, neurological outcomes and sequelae remains controversial. Blood glucose levels in the first hours of life are typically lower than normal values of older children or adults.

Clinical features attributed to hypoglycemia can be neurological/non neurological as tremors, jitteriness, irritability, seizure, lethargy, apathy, limpness, poor feeding, vomiting, apnea, weak or high pitched cry, cyanosis.[1]

Symptomatic hypoglycemia, especially if it presents with seizures, is associated with abnormal neurodevelopmental outcomes in 50% of infants. Moderate asymptomatic hypoglycemia persisting for

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3 to 5 days is also associated with 30% to 40% incidence of neurodevelopmental sequelae. Neuroimaging in infants with severe hypoglycemia shows involvement of the occipital lobes in 82%. Occipital brain injury can cause visual impairment, epilepsy and long-term disability. Cortical visual deficits are seen in a significant proportion of infants with recurrent hypoglycemia and correlate significantly with low mesial occipital apparent diffusion coefficient values on diffusion weighted MRI.[2] There is lack of concrete evidence to show the causation of adverse long term outcomes by a particular level of hypoglycemia or duration of hypoglycemia.[3]

The reported incidence of hypoglycemia varies with its definition, but it has been estimated to occur in upto 16% of large for gestation age infants and 15% of small for gestation age infants. Since blood glucose levels change markedly with in the first hours of life, it is necessary to know the baby's exact age in order to interpret the glucose level.[1]

According to "NATIONAL NEONATOLOGY FORUM, INDIA (NNF)" guidelines hypoglycemia is defined as blood glucose value of less than 40 mg/dl (plasma glucose less than 45 mg/dl).[4]

Operational threshold definition: In 2000, Cornblath recommended the use of an "operational threshold" for blood sugar management in newborn infants. The operational threshold is an indication for action and is not diagnostic of disease or abnormality and is not the goal of therapy.[5]

MATERIALS AND METHODS

This study was conducted in the department of Paediatrics, Government Medical College, Amritsar, after approval from Institutional Ethics Committee, Government Medical College, Amritsar.

This prospective study was conducted on all neonates weighing more than 1500gram admitted and found with hypoglycemia both symptomatic and asymptomatic without any other associated medical condition, known to cause brain insult at Bebe Nanki Mother and Child Care Centre, Govt. Medical College, Amritsar, between 1stJuly 2017 to 31st December 2017.

Inclusion Criteria

All neonates weighing more than 1500gram both symptomatic and asymptomatic hypoglycemia without any other medical condition known to cause brain damage.

Exclusion Criteria

All high risk neonates with symptomatic or asymptomatic hypoglycemia with known-medical condition which have potential of causing brain insult like: sepsis, meningitis, shock, perinatal asphyxia, seizures due to any cause other than hypoglycemia, inborn error of metabolism, congenital malformations and other condition affecting neurological outcome were excluded from the study.

For study purpose hypoglycemia was taken as RBS <40 mg/dl (with blood sample) recorded by Caresense II, i-SENS, Inc glucometer and confirmed by laboratory value of RBS at central laboratory of Govt. Medical College, Amritsar.

We routinely monitor RBS of at risk neonates i.e. preterm <35 weeks, IUGR, infant of diabetic mothers etc. at 1 hour, 2 hours, 3 hours and then 6 hourly for 48 hours. Any baby >1500gram found to have hypoglycemia on routine monitoring and having no other illness as described in exclusion criteria was included in the study. We confirmed hypoglycemia with venous sample laboratory value. Any other neonate who was not being monitored for hypoglycemia or outborn neonates if presents with signs and symptoms of hypoglycemia were also enrolled similarly after ruling out exclusion criteria.

35 neonates weighing >1500 grams with hypoglycemia, both symptomatic and asymptomatic were enrolled after taking written informed consent from parents/guardians. Detailed maternal and neonatal history was taken, clinical examination, anthropometry, laboratory investigations of neonates, wherever indicated were done. Neonates were managed according to the unit protocol for hypoglycemia management, duration of symptoms and daily monitoring was done for the progress.

Follow up was done in high risk neonatal follow up clinic at 3, 6, 9 months ± 7 days of corrected age for growth, neurodevelopment assessment, neurological examination and related investigations. Parents were informed to bring the patient on follow up date and reminder was sent to the parents telephonically 2-3 days prior to the follow up date.

Follow up included anthropometery for growth assessment, developmental assessment scale for Indian infants (DASII)6 for neurodevelopment assessment (DASII is an Indian adaptation of Bayley Scale of Infant Development) motor and mental quotients (MoDQ and MeDQ) were calculated as per the DASII6 instruction manual and related investigations like ultrasonography of cranium (done at discharge), MRI (done at 3 months of CGA), BERA (done at 6 months of CGA), vision assessment (done at 9 months of CGA), ROP (if required), EEG (if indicated) were done.

Data Collection and Analysis

The data from the present study was systematically collected, compiled and statistically analysed to draw relevant conclusions. The p-value was determined finally to evaluate the levels of significance. The p-value of >0.05 was considered as non significant; p-value of < 0.05 was considered as significant. The results were then analysed and compared to previous studies. SPSS-23 version of

software was used, released 2015, Armonk, NY:IBM corp, using ANOVA, Fisher exact chi square test, Unpaired T-test.

RESULTS

A total of 35 hypoglycemic neonates both symptomatic and asymptomatic were enrolled in the study, 4 (11.42%) patients died before follow up, 1 (2.85%) patient lost to follow up and follow up was possible in 30 (85.71%) cases out of which 14 (46.7%) cases were symptomatic and 16 (53.3%) were asymptomatic who were finally analysed in the study. out of symptomatic cases 3 (10%) were symptomatic females and 11 (36.66%) were symptomatic males and out of asymptomatic cases 6 (20%) were asymptomatic females and 10 (33.33%) were asymptomatic males. 16 (53.33%) cases were born via LSCS (lower segment caesarean section) and 14 (46.7%) cases were born via VD (vaginal delivery).

Clinical symptoms reported in symptomatic group in our study were lethargy and poor feeding in 11 (78.57%) cases, jitteriness in 1 (7.14%) case, seizures in 2 (14.2%) cases, seizures along with lethargy and poor feeding in 2 (14.2%) cases and apnoea along with lethargy and poor feeding was seen in 1 (7.14%) case. Lethargy and poor feeding was the most common symptom.

In our study, the prevalence of abnormal neurodevelopmental outcome according to DASII6 was 53.33% (n = 16) cases who had abnormal MoDQ (<70%) and 56.66% (n=17) cases who had abnormal MeDQ (<70%) at 3, 6, 9 months of CGA respectively.

There was statistically significant difference in the mean values of MoDQ and mean value of MeDQ (developmental quotient in % age) on follow up at 3, 6, 9 months of corrected gestational age between symptomatic and asymptomatic hypoglycemic cases. Mean MoDQ and MeDQ at 3 months of CGA was 70.78 ± 10.55 and 66.50 ± 15.46 in symptomatic cases respectively and in asymptomatic cases mean MoDQ and MeDQ was 83.06 ± 14.56 and 79.81 ± 13.79 respectively (p value 0.014, 0.019 respectively). Mean MoDQ and MeDQ at 6 months of CGA was 70.92 ± 12.92 and 64.64 ± 17.94 in symptomatic cases respectively and in asymptomatic cases mean MoDQ and MeDQ was 83.31 ± 11.88 and 81.18 ± 14.02 respectively (p value 0.011, 0.008 respectively). Mean MoDQ and MeDQ at 9 months of CGA was 67.92 ± 19.06 and 67.21 ± 19.16 in symptomatic cases respectively and in asymptomatic cases mean MoDQ and MeDQ was 83.00 ±16.44 and 81.18 ± 13.89 respectively (p value 0.02, 0.02 respectively, [Table 1]).

Out of total 14 (46.66%) hypoglycemic cases 8 (57.14%) symptomatic cases and 6 (37.5%) asymptomatic cases had microcephaly on follow up i.e. head circumference < - 3SD. There was no statistically significant difference between mean value of head circumference between symptomatic and asymptomatic cases at 3, 6, 9 months of CGA on follow up. [Table 2]

MRI was abnormal in 16 (53.33%) out of which 10 (71.4%) were symptomatic cases and 6 (37.5%) were asymptomatic cases and the difference was not statistically significant.

Ultrasonography was done in all cases at discharge and it was found abnormal in 2 (5.7%) patients. It showed ependymal cyst in 1 patient and caudothalamic cyst was present in another patient.

BERA, vision assessment was done in all cases at 6 and 9 months of CGA respectively on follow up and it was normal in all patients.

EEG was indicated in only 4 (28.4%) cases who had seizures and it was normal in all the 4 cases. [Table 3]

Table 1: Comparison of Development Status According To Development Quotient (As Per Dasii) Between Symptomatic and Asymptomatic Cases At 3, 6, 9 Months Of Cga On Follow Up

Age		Symptomatic (n=14)	Asymptomatic (n=16)	P value
3 Months CGA (n=30)	MoDQ	70.78±10.55	83.06±14.56	0.014
	MeDQ	66.50±15.46	79.81±13.79	0.019
6 Months CGA (n=30)	MoDQ	70.92±12.92	83.31±11.88	0.011
	MeDQ	64. 64±17.94	81.18±14.02	0.008
9 Months CGA (n=30)	MoDQ	67.92±19.06	83.00±16.44	0.02
	MeDQ	67.21±19.16	81.18±13.89	0.02

Table 2: Comparison of Mean of Head Circumference With Symptomatic And Asymptomatic Cases At 3 Months, 6 Months, And 9 Months Corrected Gestational Age On Follow Up.

Age	Microcephaly	Symptomatic (n=14)	Asymptomatic (n=16)	P value
3 Months CGA (n=30)	Present	35.16±1.27	35.20±0.98	0.957
	Absent	37.95±1.70	38.30±1.18	0.625
6 Months CGA (n=30)	Present	38.07±1.54	36.84±2.73	0.316
	Absent	41.26±2.01	41.24±1.15	0.978
9 Months CGA (n=30)	Present	39.40±1.70	39.20±0.87	0.815
	Absent	42.85±1.95	43.16±1.88	0.684

Table 3: Comparison of MRI, USG, BERA, Vision Assessment, Eeg (Done On Follow Up) Between Symptomatic And Asymptomatic Hypoglycaemia

		Symptomatic (n=14)		Asymptomatic (n=16)		P value
		No. of cases	% age	No. of cases	% age	
MRI	Abnormal	10	71.4%	6	37.5%	0.063
	Normal	4	28.57%	10	62.5%	
USG	Abnormal	1	7.14%	1	4.76%	0.063
	Normal	13	92.85%	15	71.42%	
BERA	Abnormal	0	0%	0	0%	-
	Normal	14	100%	16	100%	
Vision Assessment	Abnormal	0	0%	0	0%	-
	Normal	14	100%	16	100%	
EEG	Abnormal	0	0%	0	0%	-
	Normal	4	28.57%	0	0%	

Table 4: Comparison Of Baseline Characters Between Symptomatic And Asymptomatic Cases

Variable	Symptomatic (n=14)	Asymptomatic (n=16)	Total	P value
Gestation age in weeks	37.35±2.25	36.73±2.12	37.02±2.17	0.446
Birth weight in grams	2357.14±723.99	2462.50±898.79	2413.33±809.73	0.729
Head circumference at birth (cm)	32.10±2.63	32.41±1.72	32.27±2.16	0.695
Length at birth (cm)	46.70±3.71	45.93±3.15	46.29±3.38	0.548
Age at diagnosis(in days)	2.78±1.52	1.87±1.45	2.30±1.53	0.106
Blood glucose (glucometer in mg/dl)	30.07±6.06	31.50±5.84	30.83±5.89	0.517
Blood glucose (laboratory in mg/dl)	24.00±6.67	23.12±5.58	23.53±6.02	0.699
SGA	8(57.14%)	8(50%)	16(53.33%)	0.864
AGA	5(35.71%)	6(37.5%)	11(36.66%)	
LGA	1(7.14)	2(12.5%)	3(10%)	

We compared baseline variables of the enrolled cases between symptomatic and asymptomatic cases and there was no statistically significant difference in these baseline variables between symptomatic and asymptomatic. [Table 4]

There was no statistically significant difference between abnormal MoDQ and MeDQ between gender, gestation age, birth weight, age at diagnosis, level of hypoglycemia, intrauterine growth (as per Lubchenco's intrauterine growth chart)[7] in both symptomatic and asymptomatic cases. Further studies are needed to establish the relation of these variables and neurodevelopmental outcome.

DISCUSSION

Neonatal hypoglycemia is a common metabolic problem encountered in neonatal nursery and NICU and it is one of the leading cause of preventable brain damage, physical and mental handicap and early deaths among infants so it requires urgent medical intention and should be promptly and appropriately managed without delay.

In our study, the prevalence of abnormal neurodevelopmental outcome according to DASII6 was 53.33% (n = 16) cases with abnormal MoDQ and 56.66% (n=17) cases with abnormal MeDQ at 3,6,9 months of CGA respectively. These results were comparable to the previous study, done by Melana et al,[8] on 39 infants using DDST29 as a developmental tool for neurodevelopmental outcome assessment and also comparable to Chandrashekaran et al,[10] on 60 infant using DASII6 as developmental tool. We found statistically significant lower neurodevelopmental outcome (in terms of MoDQ and MeDQ) in symptomatic cases as compared to asymptomatic cases.

8 (57.14%) symptomatic cases and 6 (37.5%) asymptomatic cases had microcephaly and there was no statistically significant difference between mean value of head circumference between symptomatic and asymptomatic cases at 3, 6, 9 months of CGA on follow up and there was statistically lower neurodevelopmental outcome in cases having microcephaly in our study. This was comparable to a previous study by Duvanel et al,[11] in which they found on follow up that at 3 and 5 years of age that there was significantly lower head circumference and lower scores in psychomotor tests. Alkalay et al,[12] found microcephaly in 35% of hypoglycemic cases. In a previous study by Burns et al,[13] it was observed that head growth was suboptimal by >2 SD for one third of infants, and only 25% had head circumference values of >50th percentile in follow up evaluation.

In our study 10 (71.4%) symptomatic hypoglycemic cases and 6 (37.5%) asymptomatic hypoglycemic cases had abnormal MRI and the difference was not statistically significant. These results were comparable to Kinnala et al and Burns et al.[13,14]

Ultrasonography was done in all the enrolled cases at discharge (n=35) and it was abnormal in only 2 (5.7%) cases one from symptomatic group and another cases was from asymptomatic group. In previous study conducted by Kinnala et al,[14] who found that MRI and/or ultrasonography showed 39% evidence of abnormality in hypoglycemic infants this study also showed 10% (2 of 19) of control group had caudothalmic cysts. This contrast to our study is probably due to difference in the time of imaging done in two studies. It was done at

discharge in our study but in Kinnala et al,[14] it was done two times one in neonatal period (37-42 postconceptional week) and also 2 months later (48-51 postconceptional weeks) but both the studies state that MRI detected more abnormalities in hypoglycemic cases than ultrasonography. It has been reported in other previous studies which states the superiority of MRI over ultrasonography in detection of non haemorrhagic parenchymal lessions.[15] Sonography is lower in sensitivity in detecting cortical lessions. So parietooccipital injuries due to neonatal hypoglycemia are difficult to detect on ultrasonography.[14] However there are authors who suggest ultrasonography to be the first step in visualizing the gray and white matter abnormalities in infants with profound hypoglycemia, followed by superior detection with MRI, if needed.[16]

We did hearing assessment using BERA at 6 months of CGA and none of the patient had abnormal hearing in our study and this was similar to Chandrashekaran et al,[14] who also, did not reported impaired hearing in the cases enrolled in his study.

In our study, we did vision assessment at 9 months of CGA and none of the case was found to have abnormal vision assessment similar to the previous study done by Chandrashekaran et al,[10] but in contrast to a study by Burns et al,[13] vision abnormalities was noted in 31% of the cohort though sample size of cases enrolled by Burns et al,[13] was nearly similar to our study i.e. 35 vs 30 (in our study) but all patients enrolled by Burns et al,[13] were symptomatic and 30 (83%) patients presented with seizures i.e. symptoms with seizures 22 (61%) and seizures alone in 8 (22%) and there was family history of seizures in the case subjects but in our study only 4 (28.57%) patients had seizures out of symptomatic group of patients and none had family history of seizures in neonatal period, first degree relatives or second degree relatives and age of vision assessment was different from that of our study that was 2 years in Burns et al,[13] and 9 months of CGA in our study.

In our study only 4 (28.57%) symptomatic hypoglycemic patients had seizures as presenting symptom of hypoglycemia and EEG was done in these 4 patients and it was normal in all the 4 patients and this was in contrast to Caraballo et al,[17] who studied fifteen patients with neonatal hypoglycemia associated with epilepsy and/or posterior cerebral lesions. The difference in our study is probably due to risk factors in cases enrolled by Caraballo et al,[17] like polycythemia, low birth weight, prematurity and arterial hypertension and one patient had family history of epilepsy which was not present in our study.

In our study we found no statistically significant difference between abnormal neurodevelopmental outcome and gender and this was similar to Melana et al,[8] and Chandrashekaran et al,[10] who did not found any significant association of abnormal neurodevelopmental outcome with gender.

In the present study, we did not find significant difference between abnormal neurological outcome in relation to gestation age. This observation was similar to Melana et al,[8] and Chandrashekaran et al,[10] who did not found significant correlation between abnormal neurodevelopmental outcome and gestation age.

We found no statistically significant difference between abnormal neurodevelopmental outcome and birth weight. This observation is similar to Melana et al,[8] and Lucas et al,[18] but in contrast to Chandrashekaran et al,[10] who states the significant relationship between low birth weight and abnormal neurodevelopmental outcome.

We found no statistically significant difference between abnormal neurodevelopmental outcome and age at diagnosis of hypoglycemia but this is in contrast to Chandrashekaran et al,[10] who found lower development outcome at 1 year of CGA when any blood glucose value was ≤50 mg% in first 72 h this contrast in the study is may be due to the fact that cases enrolled by Chandrashekaran et al,[10] were low birth weight <2000g and lower in gestation age <32 weeks and sick neonates were also enrolled in the study conducted by Chandrashekaran et al,[10] i.e. patients on ventilation, requiring inotropes, packed cell transfusion, intraventicular haemorrhage grade 1 or 2, patients on parentral nutrition but all such cases were excluded from our study and any other cause known to cause brain damage was also excluded from our study and moreover we enrolled cases more than 34 weeks of gestation and > 1500gram weight to decrease the confounding effect of gestation and birth weight on neurodevelopmental outcome.

We found no statistically significant difference between blood glucose value and abnormal neurodevelopmental outcome this was similar to the study conducted by Burns et al,[13] that says that there was no relationship between the severity of hypoglycemia and neurodevelopmental outcome.

In our study we divided enrolled cases as SGA, AGA, LGA as per Lubchenco's intrauterine growth chart.[7] We found no statistically significant difference for intrauterine growth between symptomatic and asymptomatic cases (p value 0.864) and this was similar to study conducted by Mahajan et al,[19] who also did not found any significant relation of intrauterine growth between symptomatic and asymptomatic cases (p value 0.864).

In our study out of enrolled cases (n=35) we did follow up in 30 cases and 1 (2.85%) patient lost to follow up and 4 (11.42%) patients died before follow up similar to Melana et al,[8] who enrolled 42 cases and 3 (7.6%) died during follow up and 3 (7.6%) were drop outs and follow up was done in 39 number of cases and according to study conducted

by Chandrashekaran et al,[10] follow up loss was 16%. Follow up studies from India and developing countries reported 30-60% of drop out at 1-3 years of age.[20,21]

CONCLUSION

From the above observations, it can be concluded that both symptomatic and asymptomatic hypoglycemia in first week of life can lead to abnormal neurodevelopmental outcome but it is of greater severity in symptomatic as compared to asymptomatic hypoglycemia. Neonatal hypoglycemia should be considered as neonatal emergency and promptly managed to prevent any serious neurodevelopmental insult. Further regular and timely follow up is needed for age appropriate intervention to prevent permanent handicap.

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