Evaluation of Maternal and Neonatal Risk factors for Neonatal Hypoglycemia

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Abstract:

Background; Hypoglycemia is the most common metabolic disorder in the newborn.

Objectives: to identify its prevalence, risk factors, type of presentation, determine treatment schedule and prognosis.

Patient and methods: A case control study of ninety six neonates found to have hypoglycemia after screening of six hundred twelve neonates who were admitted to special care baby unit (SCBU) of child's central teaching hospital over the period between 1st of December 2007 and 30thof June 2008, and ninety six neonates were considered as control from these neonates who were admitted for other reasons but had no hypoglycemia, Blood sugar levels regarded significant in our study were less than 35 mg/dl at 1–3 hrs of life, less than 40 mg/dl at 3–24 hrs of life and less than 45 mg/dl after first 24 hrs of life. History was taken for all neonates, systemic examination and serial measurements of blood sugar was undertaken in the first 7 days of life. Packed red cell volume (PCV) was done to all neonates and blood culture was done if sepsis was a suspicion.

Results: Significant risk factors were: low birth weight, large for date, prematurity, respiratory distress, chronic maternal illnesses diabetes mellitus, perinatal asphyxia and tocolytic drug intake, The first 24 hrs of life were the most critical period for developing hypoglycemia, 43.3% of neonates were asymptomatic and 56.7% were symptomatic. The most frequent symptoms were lethargy, poor feeding, jitteriness, respiratory distress and seizure (62.5%, 26.4%, 22.9%, 20.8% and 16.6% respectively), all newborn neonates respond to treatment and nine neonates died for reasons other than hypoglycemia.

Conclusion: It is important to identify hypoglycemia in neonates with risk factors as early as possible for proper management to decrease morbidity and mortality.

Key words: neonatal hypoglycemia, maternal diabetes mellitus

Introduction:

Hypoglycemia is the most common metabolic problem occurring in newborn neonates, it is not a medical condition in itself, but a feature of illness or failure to adapt from fetal state of continuous trans-placental glucose consumption to the extra-uterine pattern of intermittent nutrient supply.[1,2,3]

Hypoglycemia is defined as glucose concentration less than two standard deviations below the mean for a particular population. [4,5,6,7]

In healthy term neonates, serum glucose values are rarely less than 35mg/dl between 1–3 hours of life, less than 40 mg / dl from 3 – 24 hours and less than 45mg /dl after 24 hours, lower glucose levels among term or preterm neonate suggest hypoglycemia. [8,9,10,11,12]

Severe or prolonged hypoglycemia may result in long term neurological damage, so the prevention of hypoglycemia is the therapeutic goal. [2]

The maintenance of normo-glycemia during the newborn period is dependent on adequate glycogen reserve, effective glycogenolysis and gluconeogenesis, an appropriate balance of insulin: glucagon and increasing postnatal nutritional intake. [9], the incidence of hypoglycemia varies with definition, population, method and timing of feeding and the type of glucose assay. [11] The overall incidences vary from 1–5 per 1000 live birth, but it is higher in at risk population. [11, 13]

The major long term sequel of severe, prolonged hypoglycemia was including; neurological damage resulting in mental retardation, recurrent seizure activity and personality disorders. [14,15,16]

Aim of the Study:

It is to find out the most critical period for developing of hypoglycemia, to find the most common type of presentation and the frequency of symptoms and signs, to identifying the risk factors associated with neonatal hypoglycemia and to determine the best treatment schedule and prognosis.

Patients and Methods:

Six hundred twelve neonates with age range of birth-7 days, who were admitted to special care baby unit of child's central teaching hospital over the period of 1st of December 2007 to 30th of June 2008, were studied for blood sugar levels, ninety six neonates with hypoglycemia were fully studied in this work. Other ninety six neonates who were admitted special care baby unit (SCBU) for other reasons with no hypoglycemia were considered as control group.

Hypoglycemia was defined as blood sugar levels less than 35 mg/dl between 1 – 3 hrs of life, less than 40 mg/dl between 3 – 24 hrs of life and less than 45 mg/dl after 24 hrs of life.

Information about all the neonates included in the study was; neonate's sex, age, birth weight, maternal illness, maternal drug intake, mode of delivery, birth asphyxia. All neonates were examined physically to asses' gestational age according to Ballard scoring system, weight, respiratory distress, cyanosis or any other signs of hypoglycemia.

Investigations included random blood sugar, packed cell volume (PCV) and blood culture; other investigations like blood gas analysis, acid base analysis, and urine for reducing substances were not

done because there were no cases of persistent hypoglycemia.

Glucometer with strips was used for screening of hypoglycemia with capillary blood samples obtained by heel prick, then a confirmatory sample (1mL of blood from a peripheral vein) to measure plasma glucose level by spectrophotometric method when the strip result was consistent with hypoglycemia or when the strip result was in the normal range but clinical findings were of hypoglycemia.

Random blood sugar (RBS) was sent for all neonates eight hourly in the first day of life starting in some of them on the first hour of life in the referring hospital, afterwards RBS was done once daily over the first week of life by researcher and medical staff on call. If it was low then confirmed by plasma sugar level and repeated 30 minutes later.

Packed cell volume was done for all neonates in the study while blood culture was done when neonatal sepsis was suspected.

All hypoglycemic neonates were treated either by enteral feeding (Breast feeding or neonate formula) in case the clinical condition of the neonates permit oral feeding and were asymptomatic, or treated by intravenous dextrose water 10% at a rate of 4–6 mg/kg/min, the neonates were followed by serial measurements of blood sugar, if hypoglycemia was a problem then the concentration of dextrose water was increased until 12% and for those not responding steroid was used (intravenous hydrocortisone 10mg/kg/24hr).

Neonatal deaths during the study were recorded.

The results were analyzed statistically using chi square P value, it is significant P if < 0.05.Odd ratio >1 increases the risk significantly, and if <1is considered protective or not significant.

Results:

During the period of 6 months of our study, the total number of admissions to SCBU was 612 neonates, hypoglycemia was found in 96 neonates (15.68%).

For those neonates with hypoglycemia we found the following results:

- Sex: male: female ratio was 1.29:1; this was statistically not significant, as shown in table (1).

Table (1): Sex difference for the study and control groups

Sex	Study group	Control group	Significance (P-value)
Male	54(56.25%)	58(60.4%)	0.553
Female	42(43.75%)	38(39.5%)	

Neonatal risk factors for hypoglycemia were studied as shown in table (2), and we found the following;

- Birth weight:
  For neonates with birth weight less than 2.5kg; the odd ratio was 2.19(1.07-4.3), with risk increased two times, and it is significant. Neonates with birth weight more than 4.34kg had odd ratio 6.92(1.37-66.7), with risk increased six times which is significant. Hypoglycemia was more in those with low birth weight (< 2.5kg) and macrosomic neonates (>4.34 kg), this was statistically significant with P value = 0.004.
- Gestational age: its effect was statistically significant (p= 0.03), with odd ratio 2.25(1.02-5.19) also significantly increased the risk two times.
- Number of gestations: it was statistically not significant (p=0.602), odd ratio 1.32(0.41-4.35) increased risk by one which is not significant.
- Hypothermia: was not significant (p = 0.701), with odd ratio1.35 (0.22-9.44), it is not significant.
- Polycythemia: it was not significant (p = 0.551), with odd ratio 0.7 (0.17-2.67) it is not significant.
- Respiratory distress: it was a significant risk factor for hypoglycemia (p = 0.003), odd ratio 3.95(1.43-12.55) the risk increased three times (significant).
- Sepsis: it was not a significant risk factor for hypoglycemia (p = 0.120).odd ratio 2.04(0.76-5.84) although two times increased the risk but it is not significant.
- Erythroblastosis fetalis: its effect was not significant (p= 0.561), odd ratio 0.49(0.01-9.69), it is not significant.
- Cyanotic congenital heart disease: its effect was not significant (p= 0.312), odd ratio 3.06(0.24-162.5), the risk increased three times but not significant.

Table (2): Neonate risk factors for hypoglycemia

Neonatal Risk factors	Category	Study group	Control group	P value	Odd ratio
* Birth weight (kg)	< 2.5	34(35.4%)	22(22.9%)	0.004	2.19(1.07-4.3)
	2.5 – 4.34	52(54.1%)	72(75%)		
	> 4.34	10(10.4%)	2(2.08%)		6.92(1.37-66.7)
* Gestational age (week)	< 37	25(26.04%)	13(13.54%)	0.03	2.25(1.02-5.19)
	> 37	71(73.9%)	83(86.45%)		
Number of gestations	Single	87(90.6%)	89(92.7%)	0.602	1.32(0.41-4.35)
	Twin	9(9.3%)	7(7.29%)		
Hypothermia	Yes	4(4.16%)	3(3.18%)	0.701	1.35(0.22-9.44)
	No	92(95.8%)	93(96.8%)		
Polycythemia	Yes	5(5.2%)	7(7.2%)	0.551	0.7(0.17-2.67)
	No	91(94.9%)	89(92.7%)		
* Respiratory distress	Yes	20(20.8%)	6(6.25%)	0.003	3.95(1.43-12.55)
	No	76(79.16%)	90(93.7%)		
Sepsis	Yes	15(15.6%)	8(8.3%)	0.120	2.04(0.76-5.84)
	No	81(84.3%)	88(91.6%)		
Erythroblastosis fetalis	Yes	1(1.4%)	2(2.8%)	0.561	0.49(0.01-9.69)
	No	95(98.9%)	94(97.9%)		
Cyanotic congenital heart disease	Yes	3(3.1%)	1(1.4%)	0.312	3.06(0.24-162.5)
	No	93(96.8%)	95(98.4%)		

Regarding maternal and perinatal factors; we found the following as shown in table (3);

- Maternal age: was statistically not significant (p= 0.733), odd ratio 1.73(0.32-11.4) for those born to mothers <16years.and those born to mothers >35 years had odd ratio 1.18(0.36-4.02) it is not significant also.
- Gravida: It was not significant, p value (p = 0.422), and no significant odd ratio for both primi and grandmulti (0.62, 1.05) respectively.
- Maternal illness:
  Diabetes mellitus: was a significant risk factor for hypoglycemia (p= 0.032), odd ratio 3.94 (1.62-6.67) significantly increased the risk three times.
  Hypertension: was statistically not significant as compared to control group (p = 0.204), odd ratio 1.94(0.62-7.667) also not significant.
- Tocolytic drug intake (Salbutamol): its effect was significant (p= 0.026), although odd ratio 0.25(0.04-0.99) which is protective.
- Type of delivery: was statistically not significant (p= 0.286), as odd ratio 0.72(0.38-1.37).
- Perinatal asphyxia: was a significant risk factor for hypoglycemia (p = 0.041).odd ratio 1.88(0.54-7.42) the risk increase one time.
- High glucose infusion during labor: it was not a significant risk factor for hypoglycemia (p=0.312), as odd ratio (0.24-162.5).

Table (3). Maternal and perinatal risk factors for hypoglycemia

Maternal risk factors	Category	Study group	Control group	P value	Odd ratio
Mother age(year)	< 16	5(5.2%)	3(3.1%)	P = 0.733	1.73(0.32-11.4)
	16 – 35	83(86.4%)	86(89.5%)		
	> 35	8(8.3%)	7(7.2%)		1.18(0.36-4.02)
Gravida	Primi	19(19.5%)	21(21.8%)	P = 0.422	0.62(0.26-1.4)
	Multi	65(67.7%)	60(62.5%)		
	Grand multi	17(17.7%)	15(15.6%)		1.05(0.45-2.47)
* Diabetes Mellitus	Yes	9(9.3%)	3(3.1%)	P = 0.032	3.94(1.62-6.67)
	No	87(90.6%)	93(96.8%)		
Hypertension	Yes	11(11.4%)	6(6.25%)	P = 0.204	1.94(0.62-7.667)
	No	85(88.54%)	90(93.7%)		
*Tocolytic drug intake (salbutamol)	Yes	3(3.1%)	11(11.4%)	P = 0.026	0.25(0.04-0.99)
	No	93(96.8%)	85(88.5%)		
Type of delivery	C.S.	29(30.2%)	36(37.5%)	P = 0.86	0.72(0.38-1.37)
	N.V.D.	67(69.7%)	60(62.5%)		
*Perinatal asphyxia	Yes	9(9.3%)	5(5.2%)	P = 0.041	1.88(0.54-7.42)
	No	87(90.6%)	91(94.7%)		
High glucose infusion	Yes	3(3.1%)	1(1.4%)	P = 0.312	3.06(0.24-162.5)
	No	93(96.8%)	95(98.9%)		

Regarding timing of hypoglycemia; sixty neonates with hypoglycemia (62.5%) presented in the first 24 hours of life, 21 neonates (21.8%) between 25–48 hr, 9 neonate (9.3%) between 49–72 hr and from 73hr–7days of life only 6 neonates (6.25%).

Signs and symptoms of hypoglycemia are shown in table (4)

Table (4): The frequency of signs and symptoms of hypoglycemia

Clinical features	No. of neonates	%
Lethargy	60	62.5
Poor feeding	25	26.4
Jitteriness	22	22.9
Respiratory distress	20	20.8
Seizure	16	16.6
Hypotonia	10	10.4
Episodes of cyanosis	8	8.3
Irritability	7	7.2
Sudden pallor	5	5.2
Episodes of sweating	3	3.1

Mode of treatment is shown in the following table (5);

Table (5): The types of therapy and the response of hypoglycemic neonates to treatment

Types of therapy	No. of neonates	%
Enteral feeding	11	11.4
Intravenous dextrose water 10% 4 – 6 mg/kg/min	69	71.8
Increase rate and concentration > 10%	12	12.5
Steroids (intravenous hydrocortisone10mg/kg/24hr)	4	4.1

Hypoglycemic neonates responded well to treatment and there was no any case of persistent hypoglycemia. Nine patients (9.37%) died probably for reasons other than hypoglycemia like sepsis, respiratory distress syndrome, asphyxia and congenital heart disease as their last blood glucose levels were normal before death.

Discussion:

Hypoglycemia was found in 96 neonates (15.68%) out of the 612 who were admitted to SCBU of child's central teaching hospital.

Our study shows that males were more affected by hypoglycemia than females, male: female ratio was 1.29:1; this result goes with that found by Cornblath M, Schwartz Rand Beozly JM [17,18]

Although hypoglycemia is more in low birth weight neonates which is attributed to the limited glycogen stores and macrosomia (>4.34kg) secondary to hyperinsulinemia, a finding is similar to McIntosh N ,Stoll BJ, Kleigman RM, and Stanley CA.[5, 11,19,20]

Preterm neonates have limited glycogen stores and didn't experience the period of rapid glycogen accumulation during late gestation and are more prone to hypoglycemia [11, 21], in this study 25 hypoglycemic neonates were premature (26.04%) and as compared with control group, prematurity appears as a significant risk factor for hypoglycemia which is similar to what was found by Stoll BJ, Kleigman RM and Stanley CA, Baker L. [11, 20]

Nine hypoglycemic neonates (9.3%) were twins and not a significant risk factor, in contrast to what was reported by, Cornblath M, Beozly JM and Stanley CA.[10, 18,20]

Lteif AN[9] and Kleigman RM[19] shows that hypothermia and polycythemia associated with increase glucose utilization that lead to hypoglycemia in the neonates and considered them as risk factors for hypoglycemia, in our study hypothermia and polycythemia detected in 4(4.16%) and 5(5.2%) hypoglycemic neonates respectively but their effect was not significant as compared to control group, this could be due to small number of sample taken during the study.

Other conditions which were found in those hypoglycemic neonates and their effect was significant as respiratory distress, this condition associated with increase glucose utilization and hypoglycemia occur once the available glycogen become inadequate to meet the increased requirement, it is compatible to what was found by Reid SR , McIntosh N , Cornblath M and Kleigman RM. [3, 5, 17, 19]

Fifteen neonate with hypoglycemia (15.6%) had sepsis, which not a significant risk factor, incompatible to what was found by Reid SR, Mclntosh N, Cornblath M & Kleigman RM.[3, 5, 17, 19]

Erythroblastosis fetalis and cyanotic congenital heart disease were found in some of our patients but their effect was of no significance, whereas Kleigman RM [19] Stanley CA [20] found that erythroblastosis fetalis lead to hyperinsulinemia in the newborns and cyanotic congenital heart disease associated with increased glucose utilization and both conditions lead to hypoglycemia in newborn neonates, this different result could be due to limited number of cases presented during this study.

Maternal age showed no significant effect on hypoglycemia and this age could reflect the reproductive age of those women and it had no relation with hypoglycemia, these findings also proved by Cole MD[6],the effect of parity also was not significant which incompatible with Cole MD.

Maternal diabetes mellitus was important risk factors for hypoglycemia in the newborn neonates[21] , this was proved by study of McIntosh N , Stoll BJ and Stanley CA. [5, 11, 20]

Maternal hypertension was not found to be a risk factor, which is incompatible with McIntosh N, Stoll BJ and Stanley CA. [5, 11, 20]

Maternal intake of salbutamol was found in 3 (3.1%) some of those hypoglycemic neonates but it's effect was a significant, as Kleigman RM[19] and Polin RA[22] considered it one of the risk factors of hypoglycemia.

Perinatal asphyxia appeared as significant risk factor among those neonates which is explained by the fact that neonates with perinatal asphyxia have depleted glycogen stores which makes them more susceptible to hypoglycemia which is also proved by Cornblath M and Stanley CA. [17,20]

Three neonates with hypoglycemia their mothers received high glucose infusion during labor and its effect on occurrence of hypoglycemia was not significant versus to report by Halamek LP. [15]

Sixty hypoglycemic neonates (62.5%) presented in the first 24 hours of life, so the maximum risk for hypoglycemia is in the first 24 hours of life, this finding is documented also by Cornblath M and Peterson B. [17, 23]

Forty two (43.3%) of hypoglycemic neonates were asymptomatic and 54 neonates (56.7%) were symptomatic, which differ from that reported by Shams S [24] (56% asymptomatic and 44% symptomatic). This is probably due to that other neonatal disorders like sepsis, asphyxia, hypocalcaemia have similar clinical features of hypoglycemia and presented in large number in the study.

The most common symptoms of hypoglycemia were lethargy (62.5%), poor feeding (26.4%), jitteriness (22.9 %), respiratory distress (20.8 %) and seizure (16.6%), the same was found by Singhal PK. [25]

Most of the patients respond to initial therapy, (11.4%) respond to oral feeding, (71.8%) required intravenous glucose infusion 10% while only (12.5%) required an increase in the concentration of dextrose water up to (12%) and (4.1 %) required the addition of steroid (intravenous hydrocortisone 10 mg/kg/24 hr) , this finding goes with what was found Singhal PK and Gomella TR[25,26]

We did not find any case of persistent hypoglycemia in those 96 hypoglycemic neonates; this could be due to the limited sample group or is not common in our locality.

Nine patients died and the cause of their death probably due to causes other than hypoglycemia because their last blood sugars were normal.

Conclusions:

Hypoglycemia is still a significant problem in our locality, the most common risk factors that increase the incidence of hypoglycemia were birth weight less than 2.5kg and more than 4.34kg, prematurity, respiratory distress, , maternal diabetes mellitus, perinatal asphyxia and tocolytic drug intake. Neonatal disorders like sepsis, perinatal asphyxia, hypocalcaemia may produce have symptoms and must not be mistaken with hypoglycemia.

Most neonates require intravenous glucose infusion for correction of hypoglycemia and small numbers of them require adjuvant therapy as steroid. Most cases of hypoglycemia are transient and treatable and there is high incidence of asymptomatic hypoglycemic cases.

Recommendations:

Good antenatal care and regular follow up of pregnant women with the risk factors like diabetes mellitus and hypertension.

Neonates who are suspected to have hypoglycemia, serial measurement of blood sugar should be performed especially during the first 24 hours of life. Feeding of neonates as early as possible to prevent occurrence of hypoglycemia and follow up of hypoglycemic neonates for it's possible sequel (neuro-developmental) is important.

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