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# Prevalence and Underlying Etiologies of Neonatal Hypoglycemia

[1]N. Najati and [2]L. Saboktakin
[1]Department of Pediatrics,
[2]Department of Endocrinology,
Tabriz University of Medical Sciences, Sina Hospital, Tabriz, Iran

**Abstract:** This study aims at determining the prevalence of neonatal hypoglycemia and its underlying causes. In this prospective study 14168 newborns delivered in Tabriz Alzahra Hospital during 2 years were evaluated in regard to blood glucose level at first 24 h of life. Glucose oxidase method with 4-amino-phenazone with a Greiner G-300 was the used method for determining the blood glucose level. Cases with blood glucose <50 mg $dL^{-1}$ were considered as hypoglycemic newborns. Underlying causes of this condition, as well as the short-term mortality rate were determined. Prevalence of neonatal hypoglycemia was 0.4% (52 newborns). Underlying causes of hypoglycemia were prematurity (61.5%), diabetic mother (13.6%), septicemia (9.6%), perinatal asphyxia (9.6%), stress (3.8%) and neonatal hyperinsulinism (1.9%). The mortality rate was 53.8%, with prematurity as the leading cause of death.

**Key words:** Blood glucose, infant newborn, prematurity, septicemia, asphyxia

## INTRODUCTION

Hypoglycemia is a common abnormality in newborns (Kinnala *et al*., 2000). It is almost 4 decades since Cornblath and Reisner described hypoglycemia as a significant cause of mortality and morbidity in newborns (Deshpande and Ward Platt, 2005). Many hypoglycemic infants remain asymptomatic. Prolonged or severe hypoglycemia causes both adrenergic and neuroglycopenic signs. Adrenergic signs include diaphoresis, tachycardia, lethargy or weakness and shakiness. Neuroglycopenic signs include seizure, coma, cyanotic episodes, apnea, bradycardia or respiratory distress and hypothermia. Listlessness, poor feeding, hypotonia and tachypnea may occur (Beers and Berkow, 2000). Delay in treatment may lead to significant neurologic consequences, such as permanent brain damage or even death (Sperling and Menon, 2004). Hypoglycemia in the newborn may be associated with both acute decompensation and long-term neuronal loss (Straussman and Levitsky, 2010; Suh *et al*., 2007; Rozance and Hay, 2006; Vannucci and Vannucci, 2001). This is mainly because of that the glucose is the major source of energy for neonate. The newborn brain depends upon glucose almost exclusively. On the other hand, the glucose regulatory mechanisms are not fully developed in newborns (Kliegman *et al*., 2007). Different conditions are in association with neonatal hypoglycemia including decreased substrate availability such as inborn errors, prematurity and intra-uterine growth retardation; hyperinsulinemia for example in infants of diabetic mother, islet cell hyperplasia, erythroblastosis fetalis, exchange transfusion, Beckwith-Wiedemann Syndrome, maternal β-mimetic tocolytic agents, high umbilical arterial catheter and abrupt cessation of intravenous glucose; other endocrine abnormalities such as pan-hypopituitarism, hypothyroidism and adrenal insufficiency; increased glucose utilization for example in cold stress, increased work of breathing, sepsis and perinatal asphyxia; and miscellaneous conditions such as polycythemia, congenital heart disease and central nervous system abnormalities (Gomella *et al*., 2009; Cloherty *et al*., 2007). Many different factors may affect the prevalence of neonatal hypoglycemia in different medical centers. So performing specific surveys in this regard is very important for a center dealing with the neonates. This study aims at evaluating the prevalence of neonatal hypoglycemia, its underlying etiologies and short-term mortality rate related to this condition in a referral center in Iran.

## MATERIALS AND METHODS

In this prospective study, 14168 newborns delivered in Tabriz Alzahra Teaching Hospital, a referral center in North-west of Iran were evaluated during their first 24 h of life. This study conducted in a two-year period between January 2009 and January 2010. Among these newborn,

**Corresponding Author:** Lida Saboktakin, Department of Pediatrics, Tabriz University of Medical Sciences, Children Hospital, Tabriz, Iran Tel: +98-914-4122542

cases with hypoglycemia were determined. The 50 mg $dL^{-1}$ was chosen as the low normal value for blood glucose. In other words, neonates with blood glucose <50 mg $dL^{-1}$ was considered hypoglycemic. For determining the blood glucose level, a standard assay was performed (glucose oxidase method with 4-amino-phenazone with a Greiner G-300) by Abbott FreeStyle™ kit, USA. For standard glucose determinations 0.5 mL venous blood (from neonate's heel) was mixed in a plastic tube with sodium fluoride and EDTA. Samples were processed within 1 h (Duvanel *et al*., 1999). Blood calcium level was also reported simultaneously by a standard method. In the cases with hypoglycemia, further evaluations were performed according to the administrating physician's order per case for determining the underlying etiology; for example, requesting for blood insulin level in cases with suspected to have hyperinsulinism, genetic evaluations in patients with possible related disorders and etc. General evaluations were thorough physical examination of mother and newborn, assessing the available documents regarding the pregnancy period events and documenting the past medical history of mothers. The mortality rate was determined by the time of discharge from hospital. The main cause of death was investigated in the expired cases. This study was approved by the Ethics Committee of Tabriz University of Medical Sciences. Statistical analysis was performed using the SPSS software (USA), version 15. The data are shown as Mean±SD or frequency (%).

## RESULTS

During the study period, 14168 newborns were delivered in this center. Eight hundred and fifty two newborn were admitted to the Neonatal Care Unit (NICU). Fifty two newborn (0.4% of all neonates, 6.1% of the NICU patients) were hypoglycemic during their first 24 h of life. In the hypoglycemic group, 28 (53.8%) patients were males and 24 (46.2%) patients were female with a male to female ratio of 1.2 to 1. Thirty one (59.6%) newborns were premature. Thirty one (59.6) newborns were LBW and 21 (40.4%) newborn were VLBW. The mode of delivery was vaginal in 41 (78.8%) patients and by cesarean section in 11 (21.2%) cases. Accompanying hypocalcemia was present in 7 (13.5%) newborns. Seizure occurred in 3 of these patients. Underlying causes of hypoglycemia are summarized in Table 1. Accordingly the most frequent cause was prematurity. The other causes were diabetes mellitus of mother, septicemia, previous asphyxia, stress and neonatal hyperinsulinism in a decreasing order. Twenty eight (53.8%) newborns expired during the hospitalization. This mortality rate is shown in

Table 1: Etiologies of hypoglycemia in the studied neonates

| Cause | Frequency (%) |
|---|---|
| Prematurity | 32 (61.5) |
| Diabetic mother | 7 (13.6) |
| Septicemia | 5 (9.6) |
| Perinatal asphyxia | 5 (9.6) |
| Stress (cold exposure) | 2 (3.8) |
| Neonatal hyperinsulinism | 1 (1.9) |

Table 2: Etiologies of mortality in hypoglycemic newborns

| Cause | Frequency (%) |
|---|---|
| Prematurity | 22 (78.6) |
| Respiratory distress syndrome | 3 (10.7) |
| Septicemia | 2 (7.1) |
| Perinatal asphyxia | 1 (3.6) |

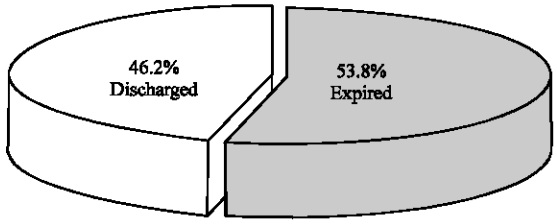


Fig. 1: Percentages of expired and discharged hypoglycemic newborns

Fig. 1. Underlying causes of mortality are summarized in Table 2. Accordingly the most frequent cause of death was prematurity. The other causes were respiratory distress syndrome, septicemia and perinatal asphyxia in a decreasing order.

## DISCUSSION

**Prevalence of neonatal hypoglycemia:** In current study, the prevalence of neonatal hypoglycemia was determined in a referral teaching center. In a 2-year period, the prevalence of this condition was 0.4% of all born neonates and 6.1% of newborns admitted to NICU during the first 24 h of life. All these hypoglycemic newborns were LBW or VLBW. The range of prevalence is varied in different reports. Johnson (2003) reported the neonatal hypoglycemia as a common problem affecting 3 to 29% of all pregnancies. As seen, the rate of current study is much less. Burdan *et al.* (2009) evaluated 2687 newborns during 2 years and reported a prevalence of 4.6% for the neonatal hypoglycemia in this series. The rate is more than 10 times higher than our result. In another study by DePuy *et al.* (2009), there were 4892 term infants weighing> 2500 g born to nondiabetic mothers over a 2-year period. One hundred and sixteen (2.4%) infants had neonatal hypoglycemia within the first 24 h of life. Although the normal term newborns have been recruited in this study, the rate is higher than ours. Summing up the mentioned

reports, prevalence of hypoglycemic newborns (whiting the first 24 h after delivery) ranges between 3 and 29% in different settings. In comparison, the relevant prevalence in our study was out of this range; i.e., the prevalence of neonatal hypoglycemia within the first 24 h after delivery was much lower than the minimum rate reported by similar studies. This difference may be justified in different ways. Employment of different definitions for hypoglycemia in infant newborns is a probable cause of heterogeneity. For example, in a study by DePuy *et al.* (2009) the prevalence of neonatal hypoglycemia was 2.4% when the recorded blood sugar was considered <50 mg $dL^{-1}$. Defining hypoglycemia using the cutoff of ≤40 mg $dL^{-1}$ reduced the prevalence in their sample population to 1.6%. In our study, the cut-off point in definition of hypoglycemia was blood glucose <50 mg/dl. So if we considered a lower cut-off point in this regard, the prevalence of the condition would more decline. But raising the cut-off point to a higher level, on the other hand, decreases probability of missing cases with milder hypoglycemia; so the mentioned approach has been considered as the main protocol in our center in this regard. The patient's health condition is considered to be another key factor in this regard (Glaser, 2000). Duvanel *et al.* (1999) evaluated 85 Small for Gestational Age (SGA) preterm newborns. The incidence of hypoglycemia in this series was 73%, which is more than our finding and the rates reported by other mentioned studies. They concluded that the prevalence of hypoglycemia differs greatly in different studies depending on the recruited population. In the term infants, they reported that the prevalence of hypoglycemia varies between 0.7 and 11.4%. It seems that the latter range is closer to our finding. It should be reminded here that 61.5% of studied newborns in our population were preterm infants. Likewise, all the hypoglycemic newborns were LBW or VLBW. It is well-known that hypoglycemia is very common in the premature infants comparing with the term newborns (Garg and Devaskar, 2006). So, other factors may contribute to the heterogeneity of reports in this regard, as well. It is assumed that the repetitional measurements for hypoglycemia during the first 24 h of life may increase the sensitivity of study by enhancing the screening power (Duvanel *et al.*, 1999). This may be a underlying factor in this regard, because we did not use a repetitional approach. On the other hand, methods of incidence calculation are rarely reported (Johnson, 2003). This may raise doubt on some reported figures in this regard. Nevertheless, the prevalence of neonatal hypoglycemia in current study was lower than that in the literature. Further studies in other similar centers may help to elucidate the issue.

**Etiology of neonatal hypoglycemia:** We also investigated possible underlying etiologies of neonatal hypoglycemia in present study. Based on our findings, the most frequent cause of hypoglycemia was prematurity. The other underlying causes were diabetes mellitus of mother, septicemia, previous asphyxia, stress and neonatal hyperinsulinism in a decreasing order. In a study by Burdan *et al.* (2009), the most frequent pathologies associated with neonatal hypoglycemia were perinatal hypoxia, neonatal hypothermia, respiratory distress, sepsis, neonatal shock and polycytemia in a decreasing order. Comparing with our findings, perinatal hypoxia, hypothermia (neonatal stress) and sepsis are mentioned in both reports with different frequencies. Hernandez-Herrera *et al.* (2006) showed an increased prevalence of asymptomatic neonatal hypoglycemia in offspring of women with diabetes mellitus in their early hours of life. As mentioned earlier, diabetic mother was the second frequent etiology of neonatal hypoglycemia in our study. To the best of knowledge, there are not other similar reports in this regard. So, conducting studies in similar centers is again highly recommended.

**Etiology of mortality:** We also assessed the underlying cause of death in neonates with hypoglycemia in present study. Surprisingly, 53.8% of these newborns expired during their hospital stay. Although it is previously concluded that the hypoglycemia is an important medical issue in neonates, to our knowledge, there is not yet a report about the exact mortality rate (Barkovich *et al.*, 1998). This is probably due to complexity of health condition in these patients. In other words, due to presence of diverse abnormalities along with hypoglycemia in these newborns, determining the exact cause of death is almost impossible. Nevertheless, this high mortality rate necessitates high caution and special cares in these infants which was the main aim of this study.

## CONCLUSIONS

Prevalence of neonatal hypoglycemia is lower than that in the literature; however, the mortality rate is considerable. So, it should be born in mind that screening is very important due to high mortality rate. Further studies in similar centers should be undertaken, because there is very limited number of reports in this regard.

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