

ORIGINAL RESEARCH ARTICLE

Neonatal Hypoglycemia: exploring incidence and risk factors

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Keywords: neonatal hypoglycemia; morbidity; risk factor, neonatal, nursing, morbidity, risk factors, public health

ABSTRACT

Introduction: Neonatal hypoglycemia is one of the most common metabolic problems in newborns, which can lead to brain damage and increase the risk of developmental delay.

Objectives: The aim of this study was to determine the incidence of neonatal hypoglycemia in neonates and to identify associated risk factors using data from one major hospital in one Province of China. The application of this study in clinical settings can help professionals early identify high risk newborn and give individualized prevention and intervention measures, which may in turn help reduce the incidence rate of neonatal hypoglycemia and reduce complications caused by hypoglycemia.

Methodology: Case control study was used on newborns who gave birth between 2016 and 2021 in China. Authors developed a case-control study at a tertiary hospital database between Jan 1, 2016 and Jan 2021. The Cases were identified on the basis of having an outcome of hypoglycemia. Four controls per case (1:4) were randomly selected. Then, multivariable logistic regression analysis was used to analyze risk factors related to the incidence of neonatal hypoglycemia.

Results: 16.8% (255) newborns in the cohort had hypoglycemia within 24 hours of birth. Besides, logistic regression analyses showed that cesarean section(OR:3.800,95%CI:8.223-23.158), maternal diabetes(OR:7.416,95%CI:4.287-12.828), maternal hypertension(OR:8.019,95%CI:3.933-16.348), small for gestational age(OR:3.894,95%CI:1.428-10.622), neonatal hypothermia(OR:17.130,95%CI:10.899-26.925) and neonatal infection(OR:17.038,95%CI:5.520-52.590) were risk factors for neonatal hypoglycemia.

Conclusion: In a contemporary cohort, The incidence of neonatal hypoglycemia is relatively high, and the incidence of neonatal hypoglycemia is significantly correlated with various clinical factors. Monitoring these risk factors is one of the important measures to reduce the adverse consequences caused by neonatal hypoglycemia.

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What do we already know about this topic?

The effect of neonatal hypoglycemia for both mother and newborn have been widely demonstrated. The incidence of the neonatal hypoglycemia after birth are higher. Identify newborns at risk of hypoglycemia after birth could allow professionals (nurses and doctors) to prioritize care.

What is the main contribution to Evidence-Based Practice from this article?

The risk factors for neonatal hypoglycemia include cesarean section, maternal diabetes, maternal hypertension, small for gestational age, neonatal hypothermia and neonatal infection. This can help us identify high-risk infants with low blood sugar early on.

What are this research's implications towards health policy?

This research can help professionals early identify high risk newborn and give individualized prevention and intervention measures, which may in turn help reduce the incidence rate of neonatal hypoglycemia and reduce complications caused by hypoglycemia.

Authors' Contributions Statement:

R.H., Y.G., and Y.L., reviewed the literature and wrote the paper. R.H. performed the statistical analyses for this study. Y.L., reviewed the quality of statistical data. Y.G., revised the focus of the discussion and reviewed the quality of the article and updated references. All authors read and approved the final manuscript.

Authors Contribution Statement: RH wrote the original manuscript and undertook the research methodology; YG: revised manuscript and data validity; YL supervised and reviewed the manuscript;

Introduction

Hypoglycemia is one of the most common metabolic disorders in newborns (Davidson et al., 2023). In recent years, with the opening of the three child policy, the improvement of birth rate, and the advancement of hypoglycemia detection technology, the incidence of neonatal hypoglycemia has shown an upward trend. It affects approximately 5-15% of newborns, which often occurs 24-48h after birth (Hosagasi et al., 2018). It has the characteristics of temporary, hidden symptoms and lack of specificity in clinical manifestations (Takagi et al., 2022), and can mostly rely on their own physiological regulation mechanism or timely breastfeeding and other intervention measures to compensate (Wight et al., 2021). Transient hypoglycemia present with a series of clinical symptom, including feeding difficulties, drowsiness, sweating, pale complexion, muscle weakness, tachycardia, etc (Gu et al., 2020). Severe cases can appear in coma, developmental delay, cognitive impairment, executive dysfunction and epilepsy and other neurological complications (Fan et al., 2020). Neonatal hypoglycemia not only affects the quality of life of newborns, but also brings

emotional distress to parents, increases their fear of hypoglycemia, and increases their care pressure (Przezak et al., 2022). Therefore, identifying factors related to hypoglycemia to improve the prognosis of hypoglycemic newborns is of great significance.

In this study, we aim to explore clinical factors associated with the incidence of neonatal hypoglycemia. In addition, multivariate Logistic regression analysis was used to analyze the risk factors of neonatal hypoglycemia.

Methods

Study Population

This is a retrospective cohort study of 1518 newborns born at a single tertiary care hospital between 1 January, 2016, and 31 January 2021. The inclusion criteria were as follow: (1) infants who have been systematically managed in our hospital since birth; (2) neonatal hypoglycemia criteria (Neonatal hypoglycemia was defined as any clinical measurement of glucose < 46 mg/dL (2.6 mmol/L) within the first half hour after birth (Tam et al., 2012). We excluded newborns with congenital disease, who were transferred to neonatal intensive care unit for any reason

except neonatal hypoglycemia. The aim of this study was to determine the incidence of neonatal hypoglycemia in neonates and to identify associated risk factors using data from one major hospital in one Province of China.

Exposures

We used multiple neonatal (gestational age, birth weight, hypothermia, neonatal asphyxia, infection, hyperbilirubinemia, polycythemia) and maternal (age, gestational age, BMI, completion of childbirth, multiple birth, maternal diabetes, maternal hypertension, anemia during pregnancy, premature rupture of membranes, meconium-stained amniotic fluid, antenatal medication use) risk factors. All predictors were based on literature review.

Outcomes

The end point was whether hypoglycemia occurred on first half hour after birth. Blood glucose is routinely monitored on capillary blood samples taken by heel-prick lance within the first half hour after birth regardless of feeds, then analyzed using the glucose oxidize method. If the initial blood glucose is lower than 2.6mmol/l, the newborn is diagnosed as hypoglycemia.

Data Analysis

Continuous clinical data are expressed as means and were compared using the independent Student t-test or rank-sum test, as appropriate. Categorical variables were compared using the Chi-square or Fisher exact test. Simple and multivariable logistic regression modeling was used to determine the associations between exposures and outcomes of selected morbidities.

Ethical and legal consideration

This study was approved by the Institutional Research and Ethics Committee of the first Affiliated Hospital of Shandong first medical

university (No.R202212210187). The data analysis procedures are in line with the guidelines in the Declaration of Helsinki. Informed consent was waived by the Ethics Committee of the first Affiliated Hospital of Shandong first medical university due to the review of the study.

Results

From 2016 through 2021, there were 1518 newborns included in the cohort. 255 newborns (16.8%) in the cohort had hypoglycemia. Based on univariate analysis of the cohort, BMI, multiple births, completion of labor, maternal diabetes, maternal hypertension, maternal anemia, premature rupture of membranes, medication during pregnancy, gestational age, low birthweight, macrosomia, small for gestational age, large for gestational age, neonatal hypothermia, neonatal asphyxia, neonatal infection were significantly associated with hypoglycemia (see supplementary material Table I). Then, we used multivariate binary logistic regression. In the multivariate analysis performed on the cohort, the following prognostic variables, cesarean section ($P<0.001$), maternal diabetes ($P<0.001$), maternal hypertension ($P<0.001$), small for gestational age ($P=0.008$), neonatal hypothermia ($P<0.001$) and neonatal infection ($P<0.001$) were found to be significantly associated with occurrence of neonatal hypoglycemia (see supplementary material Table II).

Discussion

In this study, we used a regional, retrospective, Web-based registry to gather data on newborns and their variables obtained within half an hour after birth to observe the hypoglycemia rates of newborns. Our study showed that 255 of the 1518 newborns with hypoglycemia, with an

Incidence of 16.8%, which is similar to previously reported data within the first 3 hours of life in infant (Kaiser et al., 2015). Harris (Harris et al., 2012) et al. reported an overall incidence of in 51% infants >35 weeks' gestation within the first 48h after birth, however, blood glucose concentrations measured on capillary blood samples taken by heel-prick lance and analyzed on a blood gas analyzer using the glucose oxidase method which have more sensitivity in the hypoglycemia range, therefore, our incidence may be underestimated. Moreover, previous publications have defined hypoglycemia using lower blood glucose concentrations. Pal (Pal et al., 2000) et al. defined hypoglycemia as a blood glucose concentrations <2.0 mmol/L and reported a 11% incidence in babies. Dalgic (Dalgic et al., 2002) et al. using a higher blood glucose concentration of 2.2 mmol/L to define hypoglycemia, Dalgic reported that an incidence of 9.18% in newborns at risk. Not surprisingly, our data show a higher incidence of 16.8% using a definition of a blood glucose concentration of <2.6 mmol/L. Stark (Stark et al., 2020) et al. retrospectively collected 199 infants who met the inclusion exclusion criteria for the study. They were screened for 24 hours to investigate the incidence of hypoglycemia in newborns. The study found that the incidence of hypoglycemia in high-risk infants was 27%, compared with the results of our study, which may be related to the fact that only high-risk infants were included in Stark's study. The study suggests that it is necessary to identify the high risk infants of hypoglycemia early and establish a standardized blood glucose measurement protocol in the high risk infants of hypoglycemia. Futatani (Futatani et al., 2022) et al. conducted a 10-year study of full-term newborns in Japan without risk factors for hypoglycemia. The study found that 11 cases of severe neonatal hypoglycemia occurred, six

of which occurred in non-risk newborns, This study suggests that hypoglycemia may occur even if there is no risk factor at birth, and the timing and frequency of postpartum blood glucose screening should be explored to reduce the incidence of severe pathological hypoglycemia in newborns and to avoid neonatal brain damage. Mukunya (Mukunya et al., 2020) et al. conducted a cross sectional analysis in Lira District, Northern Uganda. To investigate the neonatal hypoglycemia prevalence and risk factors, the study concluded that the incidence of neonatal hypoglycemia 2.2%, compared with our study, the incidence of low, the reasons may be related to the high rate of early breastfeeding; In addition, delayed breastfeeding and gestational age of less than 3 days are risk factors for neonatal hypoglycemia, which was not included in our study, which is a limitation of our study. This study also suggests that individualized screening and management should be enhanced for newborns less than three days of gestational age and newborns with delayed breastfeeding. Zhao (Zhao et al., 2020) et al. analyzed the clinical data of 270 newborns to analyze the risk factors for neonatal hypoglycemia. The study showed that neonatal blood glucose levels were correlated with birth term, birth weight, feeding, GDM, and hypothermia were significantly associated, similar to the results of our study. Therefore, it is important to identify risk factors for neonatal hypoglycemia early and take individualized care based on the characteristics of each newborn to reduce the incidence of neonatal hypoglycemia.

The incidence of neonatal hypoglycemia is affected by many factors. In this study, the medical records of 1518 newborns were analyzed retrospectively. Considering the statistical significance and professional significance, 17 easily available indicators were

selected for analysis. The results showed that cesarean section, maternal diabetes, maternal hypertension, small for gestational age, neonatal hypothermia and neonatal infection were risk factors for neonatal hypoglycemia in newborns.

Our study found that maternal diabetes, maternal hypertension may increase the risk of neonatal hypoglycemia, which is consistent with previous studies (Bromiker et al., 2019). Our study found that maternal diabetes and maternal hypertension may increase the risk of neonatal hypoglycemia, which is consistent with previous studies (Mitchell et al., 2020; Zhao et al., 2020). Li (Li et al., 2022) shows that offspring born to mothers with diabetes during pregnancy are associated with an increased risk of obesity and impaired metabolism of diabetes. The relationship between gestational diabetes and neonatal hypoglycemia is well known. Studies have shown that glycosylated hemoglobin levels predict the onset of hypoglycemia in newborns (Kumar et al., 2020), which is due to the fact that these newborns have higher glucose concentrations in the fetus, and the body needs to secrete more insulin in order to adapt to high glucose concentrations during the fetus. After the umbilical cord was severed after delivery, the mother stopped providing glucose, but the insulin concentration in the fetus was still high, resulting in hypoglycemia after birth (Harding et al., 2017). Moreover, some gestational age women's hyperglycemia is caused by heterozygous inactivation mutations in the gene encoding glucose sensing enzyme glucokinase (GCK), this type of newborn may respond to maternal hyperglycemia by secreting higher levels of insulin from fetuses that have not inherited the mutation from the mother, thereby increasing the risk of pregnancy related complications such as macrosomia and neonatal blood glucose

disorders (Hughes et al., 2021; Costa-Riquetto et al., 2023). Maternal hypertension is also an independent risk factor for neonatal hypoglycemia. The reason may be that hypertension leads to insulin resistance or reduces insulin sensitivity in neonates. Our study shows that cesarean delivery is also an effective predictor of neonatal hypoglycemia. Long fasting time before cesarean section, intrapartum glucose infusion, postpartum lactation delay and impaired thermoregulation are related to these factors, which is consistent with the previous studies (Ogunyemi et al., 2017; Turner et al., 2019). However, the mechanism of cesarean sections on neonatal hypoglycemia is not clear and needs further study (Cummings et al., 2022). Neonatal infection will lead to the decline of glucose storage capacity, resulting in neonatal hypoglycemia. In addition, small for gestational age infants and neonatal hypothermia are also risk factors for neonatal hypoglycemia (Stomnaroska et al., 2017; Pal et al., 2000). However, Dall'Asta (Dall'Asta et al., 2022) found in the study cohort of small and gestational age infants that diabetes in pregnancy is not related to the increase of neonatal complications, and the impact of small for gestational age infants on neonatal hypoglycemia needs further study. Early glycogen storage decreases, glucose production decreases, insulin sensitivity increases, which leads to the occurrence of neonatal hypoglycemia (Ogunyemi et al., 2017). After birth, the body temperature regulation mechanism is not perfect, will increase the body's consumption of glucose and other energy substances, reduce the ability to cope with hypoglycemia (Zhao et al., 2020), therefore, newborns should monitor body temperature in time and take measures to keep warm after delivery.

This study contributes to the literature of

neonatal hypoglycemia and their associated morbidities and builds on previous studies that have demonstrated that the risk of neonatal hypoglycemia is a function of the interaction between maternal and neonatal factors, which determine factors throughout pregnancy. Further determining the relevant factors for the incidence of neonatal hypoglycemia will help provide information for healthcare professionals seeking prevention and treatment of neonatal hypoglycemia. Developing risk based methods may improve decisions concerning the risk of neonatal blood sugar levels.

Our study has several limitations. First, these data were derived from a single institution between 2016 and 2021; second, we only considered traditional parameters and did not consider new predictors of hypoglycemia. Furthermore, due to the retrospective nature of this study, we cannot accurately obtain the

laboratory test data of pregnant women, although such indicator may have had a certain impact on blood glucose at birth.

Conclusions

In summary, our research shows that the incidence of neonatal postpartum hypoglycemia is high. Caesarean section, maternal diabetes, maternal hypertension, small for gestational age, neonatal hypothermia and neonatal infection are the influencing factors of neonatal hypoglycemia. Clinical medical staff should consider the above factors when evaluating the probability of neonatal hypoglycemia. There are limitations to this study, as the sample source is single and the representativeness is limited, which may result in information bias. Therefore, in the future, multiple conduct large-scale, multicenter, or longitudinal studies in the region.

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