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A prospective study: Risk factors and outcomes of hyperglycemia in neonates

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Abstract

Background: Hyperglycemia is a significant risk factor for morbidity and mortality among fragile infants who survive the neonatal period, with its risk inversely related to gestational age, birth weight, and clinical condition.

Objective: This study aimed to identify the risk factors and immediate outcomes associated with hyperglycemia in neonates admitted to the neonatal intensive care units (NICUs) at Ribat University Hospital and Omdurman Maternity Hospital in Khartoum State.

Methods: A prospective, descriptive, total coverage study was conducted from September 1, 2019, to February 28, 2020.

Results: Out of all neonates, 99 exhibited hyperglycemias, with 53.53% being female (female-to-male ratio of 1.1:1). The majority (95.95%) were aged 0-7 days, and 64.64% were preterm. Low birth weight was observed in 69.69% of cases. Most neonates (54.54%) had glucose levels between 150-<200 mg/dL, while 20.2% had levels >300 mg/dL. Hyperglycemia lasted between 24-<72 hours in 57.58% of cases, with a mean duration of 43.2 hours. Significant negative correlations were found with gestational age and birth weight ($r = -0.254$, $P = 0.011$; $r = -0.387$, $P = 0.00$), while a positive correlation was noted with the patients' age ($r = 0.237$, $P = 0.018$) and the use of respiratory support, antibiotics, and aminophylline ($r = 0.198$, $P = 0.05$; $r = 0.201$, $P = 0.046$; $r = 0.397$, $P = 0.00$). Neonatal sepsis was the most common diagnosis (86.86%), followed by respiratory distress syndrome (RDS) (74.74%) and hypoxic-ischemic encephalopathy (HIE) (14.14%), all showing a significant relationship with hyperglycemia ($P = 0.018$). Hyperglycemia was significantly associated with mortality (28.29%, $P = 0.04$), with higher rates observed in Omdurman Maternity Hospital (21.21%) compared to Ribat Hospital (7.08%). Most deaths occurred in critically ill patients, with RDS and HIE showing significant associations with mortality ($P = 0.037$ and $P = 0.02$, respectively). There was a negative correlation with intervention ($r = -0.368$, $P = 0.00$). The majority of cases (71.71%) were classified as transient hyperglycemia.

Conclusions: There was a high incidence of hyperglycemia among low-birth-weight infants (69.69%). Statistically significant relationships were observed between hyperglycemia and various neonatal parameters (gestational age, birth weight), risk factors (HIE, respiratory support, intravenous fluids, antibiotics, and aminophylline), and mortality. Most cases were transient, indicating that insulin intervention was generally unnecessary.

Keywords: Risk Factors; Outcomes; Hyperglycemia; Neonates

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1. Introduction

Hyperglycemia is generally defined in several ways, though there is no universally accepted safe glucose range. One definition includes whole blood glucose levels exceeding 6.66 to 6.94 mmol/L (120 to 125 mg/dL) or plasma glucose levels greater than 8.05 to 8.33 mmol/L (145 to 150 mg/dL), irrespective of the neonate's gestational age, weight, or postnatal age (Thornton et al., 2015) [1]. Another criterion specifies whole blood glucose >125 mg/dL for term infants and >150 mg/dL for preterm infants (Beardsall et al., 2010) [2]. Additionally, operational definitions of hyperglycemia in neonates sometimes include whole blood glucose levels >215 mg/dL (Hays et al., 2006) [3].

A primary concern with hyperglycemia is its potential to cause hyperosmolality, osmotic diuresis, and subsequent dehydration. Most neonatologists express concern about hyperglycemia when plasma glucose concentrations (the standard laboratory measurement) exceed 180 to 200 mg/dL (10 to 11.1 mmol/L) (Stanley et al., 2015) [4]. For every 18 mg/dL increase in plasma glucose, plasma osmolality rises by approximately 1 mOsm/L. Thus, an increase in glucose from 110 to 200 mg/dL (6.1-11.1 mmol/L) results in only a 5 mOsm/L change, which is relatively minor. In cases of hyperglycemia, the filtered load of glucose exceeds the reabsorption capacity of the renal tubules, leading to excess glucose in the urine. As glucose acts as a solute, it draws water into the urine through osmosis, resulting in osmotic diuresis and a high volume of glucose-containing urine, which can cause dehydration. The exact blood glucose level that triggers osmotic diuresis in neonates remains unclear; however, significant osmolar changes have been observed at serum glucose levels exceeding 360 mg/dL (Beardsall et al., 2010) [2].

Furthermore, preterm infants with hyperglycemia face increased risks, including higher mortality rates, infections, intracranial hemorrhage, neurodevelopmental impairments (especially with prolonged or symptomatic hyperglycemia), reductions in white matter seen on MRI, retinopathy of prematurity, and developmental delays (Blanco et al., 2006) [5]. Hyperglycemia is an independent risk factor for predicting mortality, with a 57% likelihood of death in critically ill neonates (Hays et al., 2006) [3]. In asphyxiated term infants, hyperglycemia during the first 12 hours correlates with poor gross motor outcomes. When it occurs on the first day in infants undergoing therapeutic hypothermia for hypoxic-ischemic encephalopathy, it is linked to negative outcomes (Rozance et al., 2018) [6]. Hyperglycemia is also common in infants with necrotizing enterocolitis (NEC), correlating with increased late mortality and longer NICU stays (Ibrahim et al., 2006) [7]. Continuous glucose monitoring indicates that hyperglycemia is most prevalent in the first 3 to 5 days after birth, but it can persist for up to 10 days or longer (Beardsall et al., 2010) [2].

This study aimed to identify the risk factors and immediate outcomes related to hyperglycemia in neonates admitted to neonatal intensive care units. Understanding the causes, risk factors, diagnosis, and management is essential for preventing long-term complications and improving outcomes. As protocols on neonatal hyperglycemia are frequently updated, this research seeks to enhance knowledge and practices among healthcare professionals managing this condition.

2. Methodology summary

This study utilized a prospective descriptive cross-sectional design and was conducted in a hospital setting. It was a multicenter study carried out in the neonatal units of Ribat University Hospital and Omdurman Maternity Hospital in Khartoum, running from September 1, 2019, to February 28, 2020, over a six-month period. The study included all neonates admitted with hyperglycemia during this time. Exclusions were made for neonates not admitted, those without a hyperglycemia diagnosis, cases where parents declined participation, and those with incomplete records. The study aimed for total coverage, including all admitted neonates with hyperglycemia.

Data were collected from patient records and through direct interviews using a pre-designed questionnaire, which captured personal information, weight, gestational age, risk factors, interventions, and immediate outcomes. Random blood sugar (RBS) levels were measured with a glucometer, with hyperglycemia defined as blood sugar >150 mg/dL (8.3 mmol/L). Data analysis was performed using the Statistical Package for Social Sciences (SPSS, version 26), and results were presented in tables and figures.

2.1. Study Variables

- **Independent Variables:** Sociodemographic data (age and gender), gestational age, mode of delivery.
- **Dependent Variables:** Causes, interventions, and outcomes.
- **Ethical Considerations:** The study received approval from the ethics review committee of the Sudan Medical Specialization Board, Council of Pediatrics and Child Health. Authorization was obtained from the hospital's

administrative authority, and informed consent was collected from participants while ensuring confidentiality throughout the study.

3. Results

A total of 99 patients participated in this prospective, descriptive study conducted in the neonatal units of Ribat University Hospital and Omdurman Maternity Hospital from September 2019 to February 2020.

3.1. Demographic Characteristics

Among the patients, 52.52% (n=52) were admitted to Ribat University Hospital, while 47.48% (n=47) were from Omdurman Maternity Hospital. The gender distribution showed that 53.53% (n=53) were female and 46.47% (n=46) were male, resulting in a female-to-male ratio of 1.1:1. Regarding age, 97.97% of patients experienced hyperglycemia within the first week of life, with 48.45% (n=47) in the 24–72-hour age group. The mean age of the patients was 52.6 hours. Statistical analysis indicated a significant correlation between hyperglycemia and its duration (r=0.237, P=0.018; r=0.333, P=0.01). In terms of gestational age, 64.65% (n=64) were preterm, while 35.35% (n=35) were term infants, with a mean gestational age of 33 weeks. While the relationship between gestational age and hyperglycemia was not statistically significant (P=0.059), a negative correlation was noted (r=-0.254, P=0.011).

Regarding birth weight, 69.69% (n=69) of patients had below-average weights. Specifically, 6.06% (n=6) weighed less than 1 kg, 21.21% (n=21) weighed between 1-<1.5 kg, and the majority, 42.42% (n=42), weighed between 1.5-<2.5 kg. The mean birth weight was 1.82 kg (P=0.01), with a negative correlation between birth weight and hyperglycemia duration (r=-0.387, P=0.00; r=-0.249, P=0.013). The most common mode of delivery was cesarean section (C/S) at 66.67%, followed by vaginal delivery (VD) at 32.32%, and assisted vaginal delivery (1.01%) (P=0.023) [Table1].

3.2. Maternal Characteristics

Among the mothers, 22.22% (n=22) had a history of premature rupture of membranes (PROM), with 50% experiencing PROM for >24-72 hours, although this was not statistically significant (P=0.5). Most mothers (54.54%, n=54) did not have any pregnancy-related or chronic medical conditions, and there was no statistical significance in the distribution of conditions (P>0.05). Additionally, 59.59% of mothers received medications during pregnancy, again with no significant correlation (P>0.05). Only 7.17% of infants had a family history of diabetes mellitus, but none had siblings with neonatal hyperglycemia, with all results showing non-significant P values [Table2].

3.3. Neonatal Causes of Admission

The main reasons for admission included sepsis (86.87%, P=0.2), respiratory distress syndrome (RDS) (74.74%, P=0.9), prematurity (64.64%, P=0.1), jaundice (43.43%, P=0.2), congenital malformations (22.22%, P=0.9), and hypoxic-ischemic encephalopathy (HIE) (14.14%, P=0.018). Of those with HIE, 3 (3.03%) were classified as grade 1, 6 (6.06%) as grade 2, and 5 (5.05%) as grade 3. Additionally, 5.05% were admitted with acute kidney injury (AKI), 4.04% with necrotizing enterocolitis (NEC), and 3.03% with suspected meningitis (P=0.4, 0.3, 0.7, respectively). Most patients (94.94%) received antibiotics (P=0.1), with a positive correlation observed between antibiotic use and hyperglycemia (r=0.201, P=0.046). Furthermore, 36.36% received aminophylline (P=0.02), showing a positive correlation with hyperglycemia (r=0.397, P=0.00). Other medications, including diuretics and phenytoin, were used by 15.15% and 8.08% of patients, respectively. Only 2.02% received catecholamines, and none received steroids, with no significant correlations found [Table3].

3.4. Blood Glucose Levels and Duration of Hyperglycemia

54.54% of patients had blood glucose levels between 150-<200 mg/dl, 25.26% between 200-300 mg/dl, and 20.2% above 300 mg/dl, with a mean blood glucose level of 228.9 mg/dl. The duration of hyperglycemia was predominantly 24-<72 hours for 57.58% (n=57) of patients, while 32.32% (n=32) experienced it for less than 24 hours, and 10.1% for 3-7 days. None had hyperglycemia lasting more than one week, with a mean duration of 43.2 hours [Table4].

3.5. Interventions and Outcomes

Of all patients, 49.5% received no intervention, while 28.28% had changes in fluid rates, 12.12% in fluid concentrations, and 10.1% in fluid types. None were treated with insulin. Regarding outcomes, 71.71% (n=71) experienced transient hyperglycemia, while 28.29% (n=28) did not survive, and none had persistent hyperglycemia. There was a negative correlation between interventions and mortality (r=-0.368, P=0.00) [Table5].

3.6. Mortality Rate Distribution

Out of 28 neonatal deaths, 21.21% (n=21) were from Omdurman Maternity Hospital, and 7.08% (n=7) from Ribat Teaching Hospital. Most deaths occurred in critically ill patients, with 89.2% (n=25) having RDS (P=0.037), 82.1% (n=23) with sepsis (P=0.3), and 78.5% (n=22) due to prematurity (P=0.069). Additionally, 25% (n=7) had HIE (P=0.02), with 4 classifieds as grade 3. Jaundice and congenital malformations accounted for 21.4% of the deaths each (P=0.02). All deceased patients were on respiratory support, with 35.7% (n=10) on mechanical ventilation, 28.6% (n=8) on CPAP, and 35.7% (n=10) off oxygen. A positive correlation was found between hyperglycemia and the mortality rate (r=0.232, P=0.04), with 35.71% of deaths having blood glucose levels above 300 mg/dl (P=0.04) and 17.43% experiencing hyperglycemia for 3-7 days (P=0.01) [Table5].

Table 1 Demographic Characteristics of Patients

Characteristic	Value
Total Patients	99
Hospital Admission	
- Ribat University Hospital	52.52% (52)
- Omdurman Maternity Hospital	47.48% (47)
Gender Distribution	
- Female	53.53% (53)
- Male	46.47% (46)
Mean Age (hours)	52.6
Hyperglycemia in First Week	97.97%
Hyperglycemia Duration	
- 24-72 hours	48.45% (47)
Gestational Age	
- Preterm	64.65% (64)
- Term	35.35% (35)
Mean Gestational Age (weeks)	33
Mean Birth Weight (kg)	1.82
Birth Weight Distribution	
- <1 kg	6.06% (6)
- 1-<1.5 kg	21.21% (21)
- 1.5-<2.5 kg	42.42% (42)
Mode of Delivery	
- Cesarean Section (C/S)	66.67%
- Vaginal Delivery (VD)	32.32%
- Assisted Vaginal Delivery	1.01%

Table 2 Maternal Characteristics

Characteristic	Value
History of PROM	22.22% (22)
PROM Duration (>24-72 hours)	50%
Pregnancy-related Conditions	
- No conditions	54.54% (54)
Medications During Pregnancy	59.59%
Family History of Diabetes Mellitus	7.17%

Table 3 Neonatal Causes of Admission

Cause of Admission	Percentage
Sepsis	86.87%
Respiratory Distress Syndrome (RDS)	74.74%
Prematurity	64.64%
Jaundice	43.43%
Congenital Malformations	22.22%
Hypoxic-Ischemic Encephalopathy (HIE)	14.14%
Acute Kidney Injury (AKI)	5.05%
Necrotizing Enterocolitis (NEC)	4.04%
Suspected Meningitis	3.03%

Table 4 Blood Glucose Levels and Duration of Hyperglycemia

Blood Glucose Level (mg/dl)	Percentage
150-<200	54.54%
200-300	25.26%
>300	20.2%
Mean Blood Glucose Level	228.9 mg/dl
Duration of Hyperglycemia	
- <24 hours	32.32% (32)
- 24-<72 hours	57.58% (57)
- 3-7 days	10.1%
Mean Duration (hours)	43.2

Table 5 Outcomes and Mortality Rates

Outcome	Percentage
Transient Hyperglycemia	71.71% (71)
No Survival	28.29% (28)
Hyperglycemia >300 mg/dl in Deaths	35.71%
Patients with HIE in Deaths	25%
Mean Blood Glucose in Deaths	
- Above 300 mg/dl	35.71%
- Duration 3-7 days	17.43%
Critically Ill Patients	89.2%
Patients on Mechanical Ventilation	35.7% (10)
Patients on CPAP	28.6% (8)
Patients Off Oxygen	35.7% (10)

4. Discussion

Hyperglycemia is a significant risk factor for mortality and morbidity in neonates, representing a common metabolic abnormality in critically ill infants. In our study, we identified 99 cases of neonatal hyperglycemia with a slight female predominance (53.53%). This finding contrasts with studies by Mohammed et al. (2016), Najati et al. (2007), and Gul et al. (2017), which reported a male predominance [8,9,10]. Several factors contribute to the development of hyperglycemia in neonates, particularly its increased prevalence with decreasing gestational age and birth weight, notably among extremely low birth weight (ELBW) infants. The early neonatal period, especially the first week of life, is critical, as stress can disrupt glucose metabolism, leading to hyperglycemia. Our results align with existing literature, showing that 97.97% of hyperglycemic cases occurred within the first week, with a significant correlation between the duration of hyperglycemia and patient age ($P = 0.012$) (Cameron et al., 2021; Keszler et al., 2022) [11,12].

Hyperglycemia is particularly common in extremely preterm and very low birth weight (VLBW) infants, with various studies demonstrating its association with adverse short- and long-term outcomes (Lundgren et al., 2020) [13]. In our study, 64.65% of patients were preterm, with a mean gestational age of 33 weeks. We found a negative correlation between hyperglycemia and both gestational age and birth weight ($r = -0.254$, $P = 0.011$; $r = -0.387$, $P = 0.00$). These findings support research by Akmal et al. (2017) [14] and Beardsall et al. (2010) [2], which noted significant correlations between hyperglycemia, gestational age, and birth weight. Interestingly, we found a statistically significant correlation between the mode and place of delivery and hyperglycemia ($P = 0.023$), aligning with findings from Adeniji et al. (2017) [15]. In contrast, antenatal risk factors such as maternal diabetes, premature rupture of membranes (PROM), steroid use, and family history of diabetes showed no significant association with hyperglycemia (DeSantis et al., 2020) [16].

Postnatal factors like sepsis and respiratory distress have been implicated in hyperglycemia development; however, our study did not find a statistically significant relationship, despite these conditions being common at admission. Previous studies have reported significant associations between respiratory distress syndrome (RDS) and hyperglycemia (Harrison et al., 2018) [17], emphasizing the complex interplay of factors influencing neonatal glucose metabolism. We also investigated the role of medications in hyperglycemia development. While some studies suggested that dopamine administration could reduce insulin secretion, our findings did not show a significant correlation. However, we did observe a significant association between aminophylline use and hyperglycemia ($P = 0.02$) (Sutherland et al., 2019) [18].

Feeding status did not show a statistically significant difference ($P = 0.7$), which diverges from other studies linking reduced milk intake with hyperglycemia (Yoon et al., 2015) [19]. Similarly, the type of intravenous fluids administered also lacked significant correlation ($P = 0.08$), reinforcing the notion that intravenous glucose infusion may contribute to hyperglycemia. Regarding interventions, 49.5% of patients required no treatment, while adjustments to fluid rates were made for 28.28%. Notably, 71.7% of patients recovered, although 28.29% died, with hyperglycemia identified as a significant mortality risk factor. Our results echo findings from Sabzehei et al. (2018) [20] and Gul et al. (2017) [10],

who highlighted the correlation between hyperglycemia and increased mortality risk, particularly in cases with higher blood glucose levels and prolonged duration.

A key limitation of our study is the relatively small number of fully documented records, which may hinder the identification of significant relationships. Further research with larger cohorts is necessary to strengthen these findings and explore the multifaceted nature of hyperglycemia in neonates.

5. Conclusion

Hyperglycemia is relatively common among infants admitted to the NICU and is significantly linked to increased mortality. While our study did not find a statistically significant relationship between hyperglycemia and conditions such as sepsis and respiratory distress syndrome (RDS), it did reveal significant associations between hyperglycemia and various neonatal parameters, including gestational age and birth weight, as well as risk factors like respiratory support, intravenous fluids, antibiotics, and aminophylline. Most cases of hyperglycemia were transient, so insulin intervention was often unnecessary; however, there was a negative correlation between intervention and outcomes. Critically ill patients faced a higher risk of mortality, with conditions like RDS, hypoxic-ischemic encephalopathy (HIE), jaundice, and suspected inborn errors of metabolism being significantly associated with increased mortality.

Recommendations

- **Blood Glucose Monitoring:** It is essential to monitor blood glucose levels regularly:
- Every 6–8 hours for unstable or acutely ill infants (e.g., those with respiratory distress syndrome, sepsis, or necrotizing enterocolitis).
- At least once a day for stable infants who are less than 32 weeks' gestation during their first week, those receiving parenteral nutrition, infants experiencing severe unexpected dehydration or metabolic acidosis, and those with poor weight gain despite receiving over 120 kcal/kg/day.
- **Early Intervention:** Timely and appropriate interventions based on the neonatal hyperglycemia protocol should be implemented to prevent complications and reduce mortality rates.
- **Further Research:** Additional long-term studies are necessary to evaluate the complications and long-term outcomes associated with neonatal hyperglycemia.

Compliance with ethical standards

Disclosure of conflict of interest

No conflict of interest to be disclosed.

Statement of informed consent

Informed consent was obtained from all individual participants included in the study.

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