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Neonatal hyperglycaemia in extremely preterm and extremely low birth weight infants: A report of a rare case and a review of the literature

SILVANA SAPUTRI[1-3], BERYL ALODIA[1,2,4] and MUHAMMAD HABIBURRAHMAN[1,2,5]

[1]Faculty of Medicine, Universitas Indonesia, Central Jakarta, DKI Jakarta 10430, Indonesia;
[2]Dr. Cipto Mangunkusumo Hospital, Central Jakarta, DKI Jakarta 10430, Indonesia;
[3]Bunda Mother and Child Hospital, Central Jakarta, DKI Jakarta 10350, Indonesia;
[4]Community Health Centre Mampang Prapatan, South Jakarta, DKI Jakarta 12720, Indonesia;
[5]Faculty of Medicine, Imperial College London, London SW7 2AZ, UK

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Abstract. Neonatal hyperglycaemia poses risks, and the efficacy of insulin therapy is uncertain, warranting comprehensive research and guidelines. The present study reports the case of an extremely preterm neonate with an extremely low birth weight (ELBW; <1,000 g) admitted to the neonatal intensive care unit (NICU) due to recurrent hyperglycaemic episodes (peak level, 465 mg/dl) with transient hypoglycaemia on the first day of life. The mother, a 31-year-old primiparous woman, had gestational hypertension and preeclampsia, resulting in neonatal distress at birth and the need for positive pressure ventilation for stabilisation. The condition of the baby remained stable in the NICU following resuscitation. The case described herein details the management of a neonate facing multiple stresses and metabolic challenges, including grade IV hyaline membrane disease, grade II necrotising enterocolitis and a patent foramen ovale with good heart contractility. The initial laboratory findings revealed pancytopenia. At 1 h of life, the neonate experienced hypoglycaemia (33 mg/dl), treated with a 10% bolus dextrose infusion and continuous parenteral nutrition. Glucose infusion rate (GIR) adjustments followed local guidelines. Cardiovascular support with dobutamine and dopamine addressed the low blood pressure. Subsequently, the neonate developed hyperglycaemia, requiring insulin therapy and GIR adjustments. By close monitoring and promptly intervening, the authors were able to achieve stable blood glucose levels using insulin boluses (0.1 U) and adjusting the GIR to 10.9 mg/kg body weight (BW)/min. Stable glycaemia was attained by the 4th day prior to referral, with a GIR of 12.4 mg/kg BW/min. The case in the present study highlights the challenges of managing extremely preterm infants with ELBW and emphasises effective resuscitation and NICU interventions. It was hypothesised that her refractory hyperglycaemia was caused by her underlying extremely premature neonatal condition, including inadequate insulin response, gluconeogenesis, reduced glucose transporter levels, insufficient protein intake affecting insulin-like growth factor-1 release, immature pancreas development and stress-related hormonal responses.

Correspondence to: Dr Muhammad Habiburrahman, Faculty of Medicine, Universitas Indonesia, Salemba Raya Street No. 6, Senen Subdistrict, Central Jakarta, DKI Jakarta 10430, Indonesia
E-mail: muhammad.habiburrahman51@ui.ac.id

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Introduction

Neonatal hyperglycaemia is a metabolic condition, characterised by high blood glucose levels in newborn infants. It can occur in neonates with a very low birth weight (VLBW) or an extremely low birth weight (ELBW) and those who are critically ill (1). There is no universally accepted definition or consensus on blood glucose thresholds or exposure time in the diagnosis of neonatal hyperglycaemia (2). However, it is commonly defined as blood glucose levels exceeding 125 mg/dl (6.9 mmol/l) or plasma glucose levels surpassing 150 mg/dl (8.3 mmol/l) (3).

The risk of developing hyperglycaemia increases with a lower gestational age and birth weight. The cause of this condition remains unknown; however, factors that may contribute include a poorer insulin response to glucose in preterm infants, delayed feeding and a decreased ability to suppress glucose production. Pro-inflammatory cytokines and intensive care interventions, such as the use of inotropes and corticosteroids, may aggravate insulin resistance (2). The lack of a universally accepted definition and blood glucose threshold makes it difficult to determine the prevalence of neonatal hyperglycaemia. However, recent studies conducted over the past 5 years have estimated the incidence to range from 6 to 69% (4-8). Neonatal hyperglycaemia is associated with negative consequences in extremely preterm and VLBW/ELBW neonates, including sepsis, intracranial haemorrhage, retinopathy of

prematurity (ROP), necrotising enterocolitis (NEC), the requirement for ventilator support, growth retardation and increased mortality rates (9,10).

Currently, the long-term benefits of using insulin therapy for managing neonatal hyperglycaemia are not well supported, adding to the controversy surrounding its use (11). Insulin infusion may help with maintaining nutritional intake and enhancing growth in neonates; however, there is also evidence to suggest that it can further complicate hypoglycaemia and hypokalaemia (12-14). Further documentation is necessary to improve the effectiveness of treatment approaches for neonatal hyperglycaemia. Given the potential complications associated with this condition, it is imperative to prioritise the timely assessment and implementation of effective management strategies.

A number of previous studies on neonatal hyperglycaemia have been published in Western countries (4-8,15-20). The majority of the literature on this topic can be found in books rather than clinical articles (21). Moreover, the majority of case reports tend to focus only on neonatal hypoglycaemia (22-24). Additionally, a critical gap emerges from the absence of established guidelines for treating neonatal hyperglycaemia. The current approach to defining and managing this condition heavily relies on clinical judgment (13). The absence of standardised protocols and treatment algorithms emphasises the need for comprehensive research to develop evidence-based guidelines, potentially starting with published case reports. Moreover, neonatal hyperglycaemia is challenging to treat, with numerous reports indicating poor outcomes associated with this condition (4-8).

In an aim to bridge these critical gaps, the present study describes a case of preterm ELBW neonate with hyperglycaemia. To the best of our knowledge, this is the first case report of neonatal hyperglycaemia in Indonesia. The objective is to emphasise the importance of established guidelines for managing and diagnosing hyperglycaemia, as well as to provide valuable insight into comprehensive neonatal hyperglycaemia management. The present study also discusses the effectiveness of insulin treatment in managing hyperglycaemia and explores the associated morbidity outcomes.

Case report

The patient in the present study was a female neonate born extremely preterm with an ELBW. She was delivered at 25 weeks of gestation by a 31-year-old gravida 1, para 1 (G1P1) woman via caesarean section at the Mother and Children Hospital in Jakarta, Indonesia. The birth weight of the neonate was 550 g (Fenton chart for preterm girls: between the 10 and 90th percentile), with a length of 29 cm and a head circumference of 21 cm. During this pregnancy, the mother had experienced several complications, including gestational hypertension, which was managed with methyldopa and nifedipine and preeclampsia. Upon admission, the blood pressure of the mother was 200/110 mmHg, accompanied by proteinuria (3+) and signs of liver injury (aspartate transaminase, 39 U/l; alanine transaminase, 25 U/l; gamma-glutamyl transferase, 188 U/l). There was no reported history of consanguinity. Prenatal tests for COVID-19, hepatitis B, syphilis and human immunodeficiency virus all yielded negative results. An analysis of the maternal family history revealed no significant medical conditions, while that of the paternal family revealed a history of hypertension and type 2 diabetes mellitus.

Upon delivery, the patient displayed a low-pitched cry, acrocyanosis, diminished muscle tone and a heart rate below 100 beats per minute (bpm). The appearance, pulse, grimace, activity and respiration scores registered 6 and 7 at 1 and 5 min, respectively (Fig. 1). Immediate measures, including rapid assessment, warming, drying, stimulation, airway positioning and suctioning, were undertaken. However, the patient displayed no immediate response. Subsequent positive pressure ventilation resulted in an increase in heart rate, observable bilateral chest expansion and in an improved muscle tone. Capillary refill time exceeded 3 sec, necessitating intravenous fluid resuscitation prior to transfer to a level III neonatal intensive care unit (NICU). Upon arrival at the NICU, the condition of the patient remained stable, with minimal substernal retraction noted during a physical examination. The transition from positive pressure ventilation to non-invasive motion ventilation was initiated, and the patient continued to maintain stability. The placement of an umbilical venous catheter and blood sample collection via the heel-prick method was then carried out.

A laboratory workup revealed a low erythrocyte count, thrombocytopenia and leukopenia. At 1 h of life, her fasting glucose levels were 33 mg/dl, which was defined as a hypoglycaemia episode. To address this episode, the patient was administered a 10% bolus dextrose infusion (PT Otsuka Indonesia) with a dose of 2 ml/kg body weight (BW) or 1.1 ml at a rate of 1 ml/min, followed by a continuous infusion of PG1 parenteral solution (PT Fresenius Kabi Indonesia) at a dose of 60 ml/kg BW/day (volume, 30 ml). This was administered along with lipids at 2 g/kg BW/day (volume, 5.5 ml) and a maintenance dose of 10% dextrose (volume, 3 ml). The PG1 parenteral nutrition is the standard formula in the Indonesian setting. It includes amino acids (17 ml), D40% (6.2 ml), D10% (5.3 ml), calcium (1.2 ml) and KCL (0.3 ml) (total volume, 30 ml). The glucose infusion rate (GIR) was set at 4.2 mg/kg BW/min. By the 3rd h of life, her blood glucose levels had risen to 71 mg/dl, leading to an adjustment in the GIR to 6.9 mg/kg BW/min, following the local guideline of 0-1 day of life (DOL) total parental nutrition, which allows for an increase in GIR 4-6 mg/kg BW/min (25). Total parenteral nutrition is adjusted daily based on glucose level and total solution target determined in the local guideline.

Upon monitoring for 2 h, her blood pressure was below the 3rd percentile and did not reach the target mean arterial pressure (MAP) of >30 mmHg. Monitoring MAP is the main method for assessing changes in circulatory function during the first DOL in preterm infants (26). The most commonly used criterion for hypotension is MAP <30 mmHg, based on evidence that suggests the lower limit of the blood pressure autoregulatory curve is ~28 to 30 mmHg in neonatal animal models and preterm neonates (27). It was assumed that there was a contractility disorder and it was thus decided that dobutamine at 20 mcg/kg BW/min or 44 ml/kg BW/day (rate of 1 ml/h) and dopamine 5 mcg/kg BW/min or 10.9 ml/kg BW/day (rate of 0.25 ml/h) should be used in order to provide cardiovascular support and improve blood pressure. During

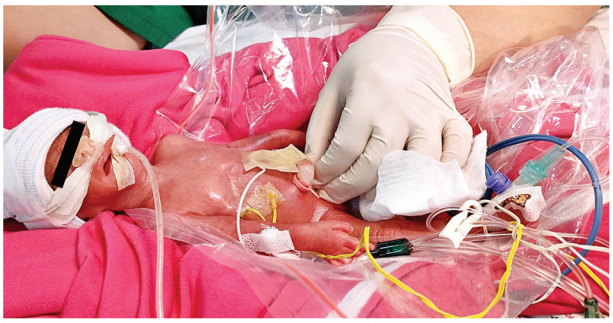

Figure 1. Immediate postnatal presentation of the preterm neonate. A female baby is depicted, born at 25 weeks of gestation with an appearance, pulse, grimace, activity and respiration (APGAR) score of 6/7 and a Ballard score of 3 (~25 weeks + 1 day), weighing 550 g. A physical examination revealed weak muscle tone, necessitating ventilation support, umbilical vein access for drug administration, and orogastric tube placement.

the hourly cardiovascular monitoring, the condition of the patient improved, prompting adjustments in medication doses according to the hemodynamic status of the patient.

Following 24 h of monitoring, her blood glucose surged to 451 mg/dl, indicating hyperglycaemia, requiring treatment with an insulin bolus of 0.1 U and GIR adjustment to 10.9 mg/kg BW/min to prevent sudden hypoglycaemia. At 1 h following the administration of insulin, her blood glucose level remained high at 465 mg/dl; thus, parenteral nutrition adjustment was made by lowering the GIR to 4.2 mg/kg BW/min, while closely monitoring the glucose level. Following the direction of the neonatologists at the hospital, if the blood glucose level of the patient were to exceed 250-350 mg/dl, bolus insulin would be administered at a dose of 0.05 U subcutaneously. If the blood glucose level was to exceed 350 mg/dl, 0.1 U insulin bolus would be administered. Blood glucose monitoring should be carried out 4-6 times per day, 2 h following insulin administration. Following insulin administration and GIR adjustments, her blood glucose levels during the hospitalization period remained <250 mg/dl; thus, no more insulin was administered. The vital signs and glucose monitoring of the patient during the hospitalization period in the NICU were recorded and are presented in Fig. 2.

During her stay in the NICU, the patient experienced a sudden apneic episode with marked substernal retraction, requiring immediate intubation. Pulmonary surfactant was administered, and a blood gas analysis revealed respiratory alkalosis (Table I). While on a ventilator, the patient remained stable with the following settings: Assist control volume guaranteed mode, tidal volume of 6 ml/kg BW (~3.3 ml), respiratory rate of 60, positive end-expiratory pressure of 5, a fraction of inspired oxygen of 21%, and an inspiration:expiration (I:E) ratio of 1:2. Volume guaranteed is a ventilation mode option that targets the tidal volume of the patient and maintains it within a normal range to prevent volume trauma. This mode of setting provides a consistent tidal volume with every inflator cycle. The main advantage of this ventilation mode is its ability to adapt to rapidly changing lung compliance due to surfactant therapy. With this setting, the baby can maintain good vital signs (oxygenation) and is well-adapted. The neonatologist adjusted the ventilator settings based on the condition of the patient, experience and clinical presentation (28,29).

The patient also received intravenous meropenem (PT Dexa Medica) at a dose of 40 mg/kg BW/dose (~22 mg twice a day) as a prophylactic antibiotic. Additionally, micafungin supplied (PT Combined Imperial Pharmaceuticals) was administered at a dose of 10-15 mg/kg BW/day (~4 mg/day) to prevent fungal infection and early-onset neonatal sepsis. Neonatal infections can lead to significant mortality and morbidity, particularly in ELBW infants, and are challenging to treat. The high prevalence of enterobacteria producing extended-range beta-lactamases in Indonesia makes meropenem particularly advantageous due to its broader antibacterial spectrum (30). This enables the use of monotherapy instead of combination therapy. Additionally, VLBW and ELBW infants have the highest incidence of *Candida* spp. fungal infection. Micafungin is the only medication approved for use in neonates by the European Medicine Agency and is effective and safe (31-33). The use of antibiotics was terminated once no infection was detected based on a laboratory assessment. The choice of empirical treatment depends on the clinical setting and local epidemiology, making it difficult to standardise therapies for VLBW and ELBW infants. The variability in clinical techniques used to treat bacterial and fungal diseases may be influenced by the lack of evidence-based guidelines.

Thoraco-abdominal radiography was also performed in the patient in the present study (Fig. 3), and this indicated grade IV hyaline membrane disease with grade II NEC. An echocardiogram revealed a patent foramen ovale with good heart contractility. Haematological analysis revealed haemoglobin levels of 15.5 g/dl, a haematocrit of 44.1%, a leukocyte count of $5.75 \times 10^3/\mu l$, and blood type O positive.

On the third day in the NICU, the patient responded well to the treatment provided. She received 80 ml/kg BW of PG2 solution, which is the same formula as PG1, but with additional normal saline. This solution is only administered when the baby is between 1 and 2 DOL. The blood glucose levels stabilised after three consecutive monitoring sessions, with levels of 119, 106 and 160 mg/dl, respectively (with a GIR of 12.4 mg/kg BW/min). However, due to socioeconomic and healthcare facility-related constraints, the baby was referred to a public hospital while in stable condition, with a blood glucose level of 78 mg/dl.

Discussion

Case reports on neonatal hyperglycaemia are limited, particularly from Indonesia. The present study found six international case reports that are summarised in Table II (15-20) and Table III (4-8). No definitive guidelines for neonatal hyperglycaemia have been established to date, at least to the best of our knowledge (10). Although the reports presented in Tables II and III did not consistently specify the definitions used, all patients in those reports had a blood glucose level >125 mg/dl (which aligns with the criteria for hyperglycaemia that we referred to American Academy of Pediatrics (AAP). The patient described herein has similarities with the cases described in the studies by Hemachandra and Cowett (16), and Muzzy Williamson *et al* (20), as all three cases involve extremely preterm infants with VLBW. In the case in the present study, the blood glucose levels were normal before escalating to hyperglycaemic levels. However, the

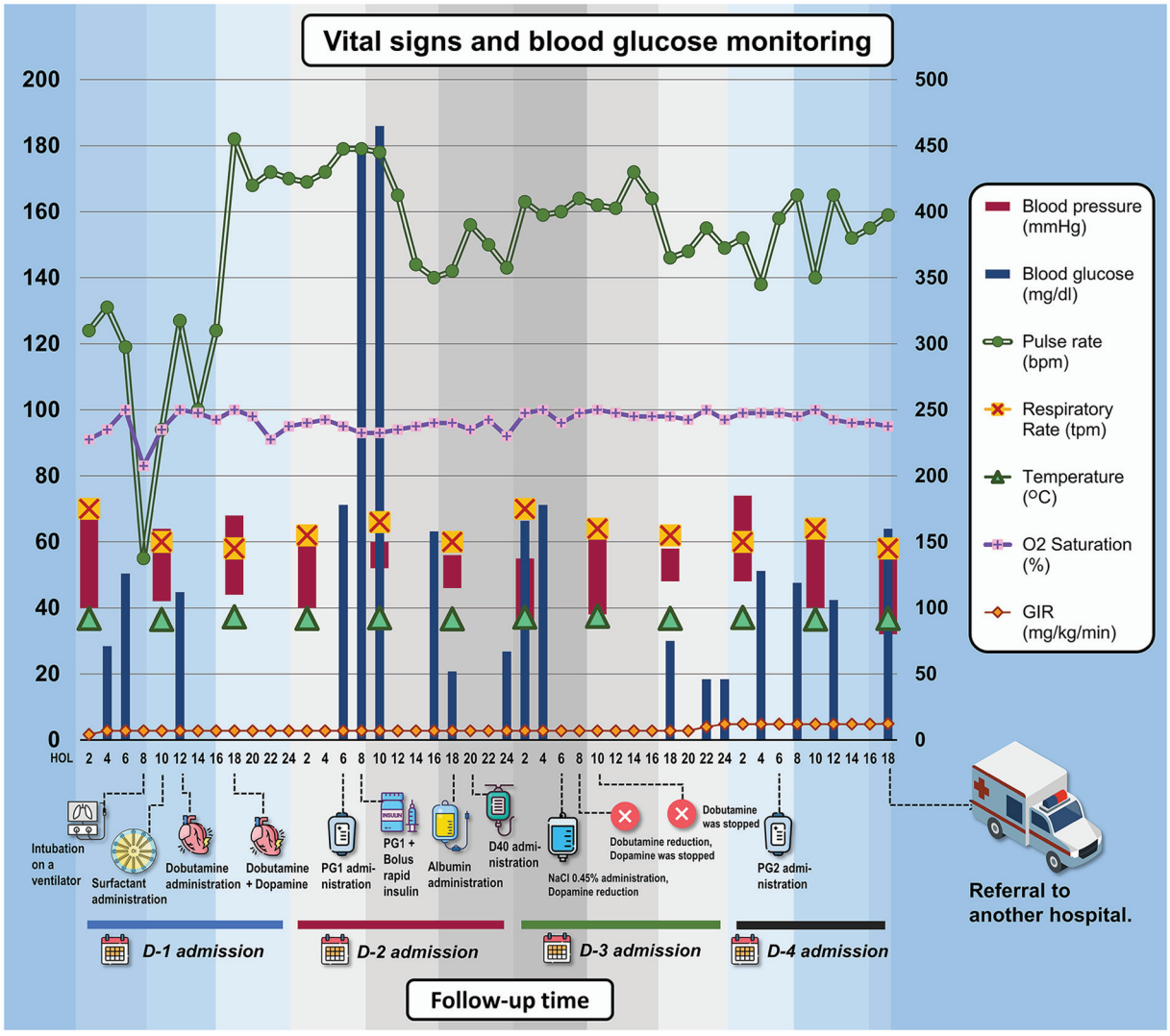

Figure 2. Vital sign monitoring of patients during hospitalization in the NICU for 4-day monitoring. There was a sudden surge in blood glucose levels during the first day of admission to the NICU, worsening the condition of the patient. The patient was admitted at 7 a.m. and received dobutamine at 10 h of life and dopamine at 18 h of life on the first day to stabilise her hemodynamic before being referred to another hospital on the 4th day. An unstable condition occurred at the 8th h of life when the patient was resuscitated and started using a ventilator. The repeated episodes of hyperglycaemia (>125 mg/dl) mostly occurred during the second day of admission, with a peak of 465 mg/dl. In the image, the parameters of blood pressure, pulse rate, respiratory rate, temperature, O2 saturation and GIR are plotted on the left y-axis, while the blood glucose parameters are plotted on the right y-axis. bpm, beats per minute; D, day; D40, dextrose 40%; GIR, glucose infusion rate; HOL, hours of life; NaCl, sodium chloride; NICU, neonatal intensive care unit; PG1/PG2, parental nutrition; tpm, times per min.

management approach used herein aligns more closely with that used in the studies by Ferguson (15), Yafi (17) and Fargas-Berríos *et al* (19). In contrast to Hemachandra and Cowett (16), Muzzy Williamson *et al* (20) and Manzar (18), who chose to reduce GIR to initiate treatment, in the present study, the authors opted to initiate insulin therapy from the beginning.

In the present study, it was not possible to evaluate the long-term results of the patient as she needed to be referred to another hospital. However, Gonzalez Villamizar *et al* (7) discovered that infants with a gestational age <32 weeks who have persistent hyperglycaemia experience a decrease in lean mass at 4 months of post-menstrual age and have unfavourable neurodevelopmental outcomes at 12 months of post-menstrual age. Zamir *et al* (6) also found that neonatal hyperglycaemia was associated with lower intelligence scores and poorer motor outcomes at 6.5 years of age. Boscarino *et al* (4) concluded that hyperglycaemia was a risk factor for motor delay.

Therapeutic approach for patients: Highlighting the use of insulin. In clinical practice, managing neonatal hyperglycaemia involves conservative and medical approaches. Conservative therapy focuses on moderating glucose intake, minimising predisposing factors, providing supportive care to alleviate stress and ensuring adequate caloric intake (11-13). On the other hand, medical therapy involves the administration of insulin to achieve euglycaemia and improve nutrient absorption. Medical intervention is necessary when blood glucose levels exceed 200 mg/dl, with a minimum 4-h interval between glucose measurements and glucosuria exceeding +2 (11-13). The strategy for treating neonatal hyperglycaemia used in the patient described herein included adjusting the GIR to maintain appropriate blood glucose levels, monitoring

Table I. Blood gas analysis results of the patient (1 h after admission) in the NICU facility.

Components	Results	Reference values of premature babies
PCO_2	21.7 mmHg	45-55 mmHg
PO_2	82 mmHg	40-60 mmHg
pH	7.465	7.28-7.32
SaO_2	97%	>80%
HCO_3^-	15.6 mmol/l	22-24 mmol/l
BE	-8 mmol/l	±2 mmol/l

PCO_2, the partial pressure of carbon dioxide; PO_2, the partial pressure of oxygen; pH, the potential of hydrogen; SaO_2, oxygen saturation; HCO_3^-, bicarbonate ion; BE, base excess. Values in bold font indicate abnormalities.

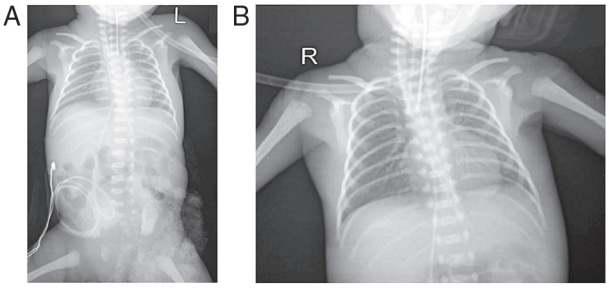

Figure 3. Radiological improvement in the chest X-ray of the patient pre- and post-surfactant administration. (A) Initial chest X-ray shortly after birth, prior to surfactant administration, illustrating low lung volumes and air bronchograms indicative of hyaline membrane disease. (B) Subsequent chest X-ray, at 11-12 h post-surfactant administration (4 ml/kg BW followed by 3 ml/kg BW), illustrating enhanced lung expansion, improved aeration and reduced lung opacities. BW, body weight.

blood glucose and administering insulin treatment. Following 2 h of insulin treatment, the blood glucose level remained <250 mg/dl.

The initial step in addressing neonatal hyperglycaemia is evaluating the GIR. The GIR can be lowered by adjusting the infusion rate or the intravenous dextrose concentration. With continuous glucose monitoring, reductions in GIR typically occur gradually, ranging from 1-2 mg/kg BW/min every 2 h, until a GIR of 4 mg/kg/min is reached or until the dextrose concentration is lowered to a minimum of 5% (11,12). In the case that a low GIR (4 mg/kg BW/min) persists with hyperglycaemia, this may indicate relative insulin shortage or insulin resistance. The consideration for insulin administration occurs when blood glucose levels exceed 250 mg/dl and urine glucose has a reading of 2+ or higher in two samples collected at intervals of at least 4 h (12). Insulin can be administered by adding it to maintenance fluids or by administering it independently. Bolus insulin administration is rarely used due to the increased risk of hypoglycaemia (11). Initial insulin infusion dosages typically range from 0.01 to 0.05 units/kg BW/h, with adjustments made based on blood glucose levels in increments of 0.01 units/kg BW/h. The maximum dosage allowed is 0.1 units/kg BW/h, with the treatment goal being to maintain blood glucose levels between 100 and 150 mg/dl (11,34).

In neonates, the initial intravenous glucose administration is maintained at a rate of 5-8 mg/kg BW/min to maintain blood glucose levels within the normal range. Blood glucose levels are typically checked every 4-6 h, although during the initial insulin administration, they can be checked, every 2-3 h to prevent prolonged episodes of low blood sugar. In the case that blood glucose levels exceed 145 mg/dl (8 mmol/l), a urine glucose examination is necessary (12,35). If glycosuria exceeds +1, the infant is at risk of increased osmolality, which can lead to excessive urination and weight loss. In such cases, adequate fluid therapy and frequent glucose monitoring (every 1-2 h) are necessary (12). Recent studies have shown the effectiveness of continuous glucose monitoring (CGM) in regulating glucose levels and reducing the risk of both high and low blood sugar in preterm infants (5,14). In the case in the present study, CGM was commenced after a hyperglycaemic episode that reached 451 mg/dl and peaked at 465 mg/dl. Following 3 h of CGM, the glucose levels stabilised. The NICU team used CGM to prevent further hyperglycaemic events, in line with the findings of the study by El-Shimi *et al* (5) on the management of hyperglycaemia.

Reflecting on the case described herein, caution needs to be exercised due to the possibility of unexpected low blood sugar levels (sudden episode of hypoglycaemia) when insulin is administered continuously (3). The risk of hypoglycaemia is a concern, particularly in ELBW newborns, where insulin pharmacokinetics may be unpredictable (35). This can be prevented by regularly monitoring blood glucose levels. In the case that hypoglycaemia occurs, insulin infusion must be discontinued and treated with dextrose 10% boluses (2 ml/kg BW) (3). At this point, the strategy of adjusting GIR to prevent hypoglycaemia during the initial administration of insulin should also be considered. The rationale for this lies in the ongoing debate surrounding the efficacy of insulin therapy for neonatal hyperglycaemia. The justification for administering insulin in the context of hyperglycaemia management in newborns, while simultaneously adjusting GIR to prevent sudden hypoglycaemic episodes, stems from the need to balance glycaemic control without risking hypoglycaemia. Adjusting GIR allows for the fine-tuning of glucose delivery to maintain blood glucose levels within a safe range while insulin works to lower elevated levels. This approach aims to prevent sudden drops in blood glucose concentration, thereby minimising the risk of hypoglycaemia. By closely monitoring blood glucose levels and adjusting GIR accordingly, optimal glycaemic control can be achieved, while mitigating the potential adverse effects of insulin therapy, such as hypoglycaemia (35). Hypokalaemia is also observed with insulin treatment and can be prevented by periodic laboratory monitoring for electrolytes. Hypokalaemia should be managed with adequate potassium supplementation (3).

Risk factors of hyperglycaemia and its impact on clinical outcomes. Previous studies have demonstrated that neonatal hyperglycaemia is more common in newborns with a birth weight of ≤1,500 g (4,7,16,20), with only two studies documenting this in a ELBW infant, similar to the case in the present

Table II. Summary of findings of case reports of hyperglycaemia among neonatal patients published worldwide.

Author(s), year of publication (country)	Sex	Age	BW	Defining case	Treatment	Outcomes	(Refs.)
Ferguson, 1967 (UK)	M	Full term	2,510 g	• Hyperglycaemia onset: 5th DOL. • Post-FBG levels: 200-250 mg/dl, with concurrent positive proteinuria. • FBG remained normal, leading to insulin withholding.	On 10th DOL, insulin initiation: 1 unit 3 times daily, escalating to 2 units 8 times daily after 1 week	Following the initiation of insulin therapy, rapid weight gain occurred. After 11 days, a gradual reduction in insulin dosage was implemented.	(15)
Hemachandra and, Cowett, 1999 (USA)	M	26 weeks	900 g	Serum glucose level (unexplained: Fasting/random) on 3rd DOL exceeded 250 mg/dl, with positive glycosuria.	Despite reducing GIR by lowering dextrose concentration (from D10% to D5%) and decreasing rate (from 16 mg/kg BW/min to 12 mg/kg BW/min), glucose concentrations remained elevated at 320 and 410 mg/dl. Consequently, insulin treatment initiated at 0.05 U/kg BW/h.	On 4th DOL, infant received intravenous insulin, tolerating total parenteral nutrition with 5% dextrose at 12 mg/kg BW/min and 2 g/kg BW/day amino acids through a CVC. Glucose concentrations maintained within 100-159 mg/dl range.	(16)
Yafi, 2014 (USA)	M	37 weeks	1,565 g	• Initial blood glucose levels (unexplained: Fasting/random): 85, 81 and 91 mg/dl. • Initial central glucose level: 175 mg/dl. • By 24 HOL, central glucose levels rose to 697 and 843 mg/dl.	Insulin administration commenced at 25 HOL at a rate of 0.1 U/kg BW/hour. On the 7th DOL, the patient initiated breastfeeding supplemented with formula. The insulin drip was transitioned to a basal-bolus subcutaneous insulin regimen normalized with feedings.	Blood glucose levels were maintained within the range of 150-200 mg/dl.	(17)
Manzar, 2015 (USA)	M	38 weeks	N/A	Initial blood glucose (unexplained: fasting/random) exceeded 200 mg/dl.	The GIR was subsequently reduced to 2.6 mg/kg BW/min.	The blood glucose level normalized within 24 h.	(18)

Table II. Continued.

Author(s), year of publication (country)	Sex	Age	BW	Defining case	Treatment	Outcomes	(Refs.)
Fargas-Berríos *et al*, 2015 (Puerto Rico)	F	39 weeks	2,041 g	• Initial blood glucose: 65 mg/dl (unexplained: fasting/random) • Following milk formula feeding, blood glucose levels rose to 206-385 mg/dl	Continuous intravenous regular insulin infusion commenced on the 13th HOL and ceased upon achieving adequate glycemic control (104 mg/dl).	• In NICU, blood glucose levels rose to 320-415 mg/dl, initiating continuous IV regular insulin infusion (0.1 U/kg BW/h). • Due to hypoglycaemia, insulin infusion discontinued, and carbohydrate infusion increased. Subsequently, insulin *lispro* injection at 0.5 U given if blood glucose exceeded 200 mg/dl. • Blood glucose ranged from 46 to 286 mg/dl over next 3 days, with adequate glycemia achieved at 5 WOL.	(19)
Muzzy Williamson *et al*, 2020 (USA)	F	23 weeks + 2 days	520 g	• Blood glucose (unexplained: fasting/random) on 3rd DOL: 180 mg/dl, with GIR of 4.2 mg/kg BW/min. • By 8th DOL, blood glucose levels persisted above 190 mg/dl despite reduced GIR (3.6 mg/kg BW/min).	Insulin infusion was initiated at a concentration of 0.25 U/ml in 0.9% NaCl, administered at a rate of 0.02 U/kg BW/h.	On 9th DOL, blood glucose reached 250 mg/dl despite continuous IV regular insulin at 0.12 U/kg BW/h and GIR of 4.1 mg/kg BW/min.	(20)

BW, body weight; F, female; M, male; CVC, central venous catheter; D, dextrose; DOL, day of life; FBG, fasting blood glucose; GIR, glucose infusion rate; HOL, hour of life; IV, intravenous; NICU, neonatal intensive care unit; WOL, weeks of life.

Table III. Summary of findings of epidemiological research on hyperglycaemia among neonatal patients published worldwide in the last 5 years.

Author(s), year of publication (country)	Study design	Population/sample	Hyperglycaemia definition	Prevalence	Treatment	Outcomes	(Refs.)
Villamizar *et al*, 2020 (USA)	Retrospective cohort	97 Infants <32 weeks GA, <1,500 g BW, admitted to the NICU, University of Minnesota Masonic Children's Hospital from February, 2012 to June, 2016.	• Blood glucose levels >150 mg/dl (>8.3 mmol/l) • Patients grouped by hyperglycaemia duration: 0 days, 1-4 days, ≥5 days.	48.5%	Adjustment of GIR without insulin mentioned.	≥5 days of hyperglycaemia negatively associated with fat mass and fat-free mass z-scores at discharge, and fat-free mass z-scores at 4 months corrected age. Persistent hyperglycaemia was also associated with impaired neurodevelopment at 12 months corrected age.	(7)
Adeniji *et al*, 2020 (Nigeria)	Cross-sectional	300 Neonates were admitted to the special care baby unit at Wesley Guild Hospital.	Blood glucose levels ≥126 mg/dl (≥7.0 mmol/l).	6.0%	N/A	Neonatal hyperglycaemia was associated with parental low socioeconomic class, maternal lack ofANC, vaginal delivery, grand multiparity, outborn status, respiratory distress, probable sepsis, and neonatal anaemia. Respiratory distress and probable sepsis independently predicted hyperglycaemia. Hyperglycaemia was significantly associated with mortality.	(8)
Zamir *et al*, 2021 (Sweden)	Retrospective cohort	533 Preterm infants <27 GA with complete glucose measurements and insulin therapy data available during the first 28 DOL	Hyperglycaemia was categorised as: • >8 mmol/l (>145 mg/dl), • >10 mmol/l (>180 mg/dl), • >12 mmol/l (>216 mg/dl), or • >14 mmol/l (once or on 2 or 3 consecutive days during the first 28 DOL.	69%	No standardised insulin protocol; insulin treatment was given based on clinical judgment.	Neonatal hyperglycaemia (>8 mmol/l) was linked to lower intelligence scores and worse motor outcomes at 6.5 years of age. Insulin treatment was not associated with improved or worsened neurodevelopmental outcomes.	(6)

Table III. Continued.

Author(s), year of publication (country)	Study design	Population/sample	Hyperglycaemia definition	Prevalence	Treatment	Outcomes	(Refs.)
Boscarino *et al*, 2021 (Italy)	Prospective cohort	280 Preterm infants <32 weeks GA or <1,500 g BW	Hyperglycaemia was defined as 2 consecutive blood glucose levels >10 mmol/l (>180 mg/dl) at least 3 h apart.	29%	Moderate hyperglycaemia was treated by reducing IV glucose concentration. Severe hyperglycaemia was managed with insulin nfusion, titrated every 4 h to maintain blood sugar <180 mg/dl.	Hyperglycaemia was identified as a risk factor for motor delay.	(4)
El-Shimi *et al*, 2022 (Egypt)	Prospective cohort	125 low birth weight neonates (<2,500 g BW)	• Mild hyperglycaemia 151-180 mg/dl • Moderate hyperglycaemia: 181-210 mg/dl • Severe hyperglycaemia: >210 mg/dl.	24%	Moderate hyperglycaemia was treated by decreasing GIR. Insulin therapy was initiated if hyperglycaemia >200 mg/dl despite GIR reductions.	Hyperglycaemia in low-birth-weight infants was linked to morbidity and mortality. Insulin treatment may be associated with hypoglycaemic episodes and mortality.	(5)

ANC, antenatal care; BW, body weight; DOL, day of life; GA, gestational age; GIR, glucose infusion rate; IV, intravenous; NICU, neonatal intensive care unit.

study (16,20). The increased incidence of hyperglycaemia in relation to a lower birth weight may be attributed to various factors, such as increased glucose synthesis, low insulin levels, reduced insulin receptor sensitivity or resistance, and the effects of counter-regulatory hormones such as catecholamines (10). The study by Hays *et al* (36) found that >50% of neonates consistently had high blood glucose levels >150 mg/dl during their first week of life (WOL). Additionally, the prevalence of hyperglycaemia between 2 and 7 DOL was documented as 32% when using a cut-off value of 250 mg/dl and increased to 57% when considering a threshold of 150 mg/dl (5,36). In the case described herein, the infant developed hyperglycaemia on the second day after birth, which then decreased following insulin administration. It is worth noting that the infant continued to experience repeated episodes of hyperglycaemia until the end of hospitalisation, although these were interspersed with intermittent episodes of hypoglycaemia.

A study in Tokyo, Japan examined the factors affecting hyperglycaemia in ELBW in the first 14 DOL (37). That study found significant associations between hyperglycaemia and various parameters. Specifically, factors such as gestational duration, birth weight, chorioamnionitis and postnatal glucocorticoid use were identified as key factors influencing the outcome (37). Additionally, maternal preeclampsia, the premature rupture of membranes and antepartum haemorrhage have also been found to be notable risk factors for hyperglycaemia (5). The link between maternal preeclampsia and elevated blood sugar levels in newborns may stem from hypertensive mothers having a greater chance of delivering infants with a lower birth weight and premature birth. These conditions are known to be associated with hyperglycaemia, as also observed in the case described herein (36). Both normoglycemic and hyperglycaemic infants can experience respiratory distress and sepsis. The latter often requires intensive medical intervention, such as multiple antibiotics, inotropic support and reliance on respiratory assistance, particularly mechanical ventilation. The case described in the present study reinforces the understanding that ELBW infants and those born extremely premature face increased morbidity when hyperglycaemia is present.

It was hypothesised that refractory hyperglycaemia in the patient in the present study was caused by the high-stress metabolic and physical condition, which resulted in damage to the β-pancreatic cells of the premature baby. Generating an adequate reserve of β-pancreatic cells through neogenesis and proliferation during the neonatal period is crucial for the long-term prevention of the development of type 2 diabetes later in life (38). Preterm newborns have a higher incidence of hyperglycaemia compared to full-term neonates. The precise mechanisms involved are not yet fully understood, but they may include issues such as insufficient insulin response to glucose, failure to suppress gluconeogenesis, reduced glucose transporter levels and insufficient protein intake leading to decreased insulin-like growth factor-1 release. Insulin-like growth factor-1 typically regulates blood glucose levels by enhancing glucose utilisation in peripheral tissues, promoting glycogen synthesis and inhibiting glucose production in the liver. Inadequate amino acid intake hampers pancreas development and insulin secretion. Ill neonates often exhibit reduced insulin production and sensitivity due to immature or less responsive peripheral receptors. Additionally, the increased production of counter-regulatory hormones such as adrenaline and cortisol due to heightened stress can contribute to hyperglycaemia in these newborns (12).

Neonatal hyperglycaemia is a significant concern, particularly for extremely preterm infants with a ELBW (<1,000 g), as it has been linked to severe complications that can markedly increase mortality rates. The study by Hays *et al* (36) underscores the substantial influence of blood glucose levels on both early mortality and the occurrence of severe intraventricular haemorrhage (IVH). A significant cerebral haemorrhage can disrupt normal brain metabolism, leading to reduced glucose consumption and the development of hyperglycaemia. Therefore it is clear that cerebral bleeding may manifest both a cause and result of hyperglycaemia (36). The impact of neonatal hyperglycaemia extends beyond IVH and includes complications, such as ROP, NEC, increased oxidative stress and susceptibility to sepsis. These complications not only result in prolonged hospitalisation but also have the potential to hinder physical growth, which can be noticeable up to two years beyond the corrected age (5). Hyperglycaemia may also exacerbate the likelihood of developing sepsis and dysfunction of multiple organs in infants with VLBW (5). For this reason, in the case described herein, in addition to the management of hyperglycaemia, we antibiotics and antifungals were also administered to prevent neonatal sepsis, as well as to stabilise the haemodynamics of the patient as the patient had a history of cardio-pulmonary disorder. Moreover, in a 2021 Indonesian report, a significant prevalence of early-onset neonatal sepsis was noted, with 52 out of 492 inborn neonates (10.6%) diagnosed with culture-proven neonatal sepsis (30). Additionally, a 2023 Indonesian study analysing 5,439 blood cultures found Gram-negative bacteria, particularly *Klebsiella* spp. and *Acinetobacter* spp., to be the predominant causative pathogens for neonatal sepsis in Indonesia, with a prevalence of 35 and 19%, respectively (39).

Discussing the long-term impact of clinical outcomes, ongoing debates exist regarding the associations between hyperglycaemia in extremely preterm infants and their long-term brain development. Subsequent studies conducted during their school-age years indicate that children in the tightly regulated blood glucose group have a similar survival rate and no abnormalities in their brain development compared to those in the standard blood glucose group (3,4,40). However, noticeable differences in height and body composition are evident, suggesting the multifaceted impact of hyperglycaemia on various aspects of growth and development (3,4,40).

Clinical implications and prevention strategies. Hyperglycaemia is a progressive disease and often involves repeated episodes in extremely preterm newborns, with negative clinical implications on their short and long-term health. Preterm infants with a low birth weight are at higher risk of developing hyperglycaemia, which is usually detected in the first WOL. Although in the majority of cases, this is resolved within a few days, some infants may experience hyperglycaemia for up to 10 days. While less common than hypoglycaemia, hyperglycaemia is associated with increased morbidity and mortality rates (5,8). Prolonged hyperglycaemia can worsen these outcomes; however, early evaluation and treatment can help mitigate its effects. Neonatal hyperglycaemia can lead to early mortality and is associated

with a higher risk of severe IVH, respiratory distress syndrome, sepsis, NEC, bronchopulmonary dysplasia and periventricular leukomalacia (41). In the present study, blood glucose level of the newborn rose to 451 mg/dl on the first day of life. Given these findings, it is critical for general practitioners, paediatricians and neonatologists to be diligent in identifying and managing hyperglycaemia in order to improve overall prognosis.

To prevent the incidence and recurrence of hyperglycaemia in neonates, several effective strategies have been identified based on the literature. Increasing protein intake in parenteral nutrition has been shown to be associated with a decrease in the occurrence of hyperglycaemia in ELBW and VLBW infants. Consuming amino acids at a daily rate of 4 g/kg BW/day can reduce the likelihood of developing hyperglycaemia by 67% compared to a daily intake of 2.5 g/kg BW (42). Amino acids, particularly arginine and glutamine, have a positive impact on glucose control by enhancing insulin secretion. Implementing strict glycaemic control, increasing intravenous fat administration, initiating enteral feeding early, and achieving full feeding faster all contribute to reducing the likelihood of developing hyperglycaemia (43-47).

A 2011 Cochrane review advised against the use of insulin as a preventive measure (48). In a multicentre study on 195 ELBW infants (49), a reduction in the risk of hyperglycaemia was observed when a continuous insulin infusion at a rate of 0.05 units/kg BW/h was administered during the initial week after birth. However, this approach also increased the risk of hypoglycaemia and mortality within 28 days, when compared to standard neonatal care (49). The criteria for initiating insulin treatment vary significantly. The standard initial dosage ranges from 0.05 to 0.1 units/kg BW of regular insulin. Neonatologists typically begin with a concentrated dose (bolus) and then switch to a continuous infusion of 0.01 to 0.05 units/kg BW per hour if high blood glucose levels persist (3). As part of clinical judgment, the metabolic clearance rate of insulin is known to be higher in preterm newborns compared to full-term infants or even adults, which may require higher rates of insulin infusion. A previous study found that normal blood glucose levels could be reached within an average of 31.4 h following the initiation of insulin therapy (50).

The optimal target glucose range for extremely preterm newborns is uncertain. A survey of clinical directors in New Zealand and Australia revealed a wide range of desired blood glucose levels, from 54 to 144 mg/dl (3 to 8 mmol/l) (50). In a randomised trial involving premature infants born before at 30 weeks of gestation or with a birth weight <1,500 g, maintaining blood glucose levels between 72 and 108 mg/dl (4 and 6 mmol/l) led to improved weight gain and head growth until 36 weeks of postmenstrual age (45). By contrast, maintaining blood glucose levels between 144 and 180 mg/dl (8 and 10 mmol/l) has been shown to not result in a similar improvement in linear growth (50).

Limitations, challenges and future directions. The present study was limited by the inability of the clinical setting to fully identify the specific factors contributing to neonatal hyperglycaemia. This limitation also applies to diagnostic methods, such as insulin testing, pancreatic radiological imaging, and, in some cases, even biopsy. As a result, the patient was transferred to a public hospital offering better care after achieving stabilisation at the authors' primary-level healthcare institution. Another limitation was not having access to the complete medical records of the referral hospital; only a brief report was provided following the release of the patient. However, it is noteworthy that this case report effectively depicts the presentation of neonatal hyperglycaemia from the standpoint of initial management and highlights the rare occurrence of such a condition after birth. As a future direction, a prospective follow-up study is warranted in order to determine the prognosis for the development of very preterm infants with hyperglycaemia (41).

In conclusion, the case described in the present study highlights the importance of the early management of neonatal hyperglycaemia. It is crucial to effectively treat hyperglycaemia in neonates from the beginning, although it remains challenging to manage. Treatment is primarily based on the clinical judgment of the physician, and the most commonly used approach is to reduce the GIR and/or administer insulin. It is hoped that this case serves as a valuable lesson for general practitioners and paediatricians treating ELBW hyperglycaemia cases, particularly in extremely premature babies. Further extensive studies are required to develop standardised protocols and treatment algorithms for neonatal hyperglycaemia to enhance patient outcomes.

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Availability of data and materials

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Authors' contributions

MH served as the principal investigator for this study, conceived the case report and made the decision to publish it. SS, BA and MH took full responsibility for the work. SS, BA and MH jointly designed the methodology and formal analysis. SS and BA curated the data and conducted the investigation. SS, BA and MH had complete access to the literature data, contributed to the analysis, drafted the manuscript, and validated all evidence analyses. MH utilised software to create visualizations of the study findings, secured funding and managed the project. Additionally, MH provided resources and supervised the study process meticulously. All authors critically reviewed the manuscript for significant intellectual content, and have read and approved the final version for publication. SS, BA and MH confirm the authenticity of all the raw data.

Ethics approval and consent to participate

Patient consent was obtained from the parents of the infant described herein, and all images and data for publication were consented according to the principles of the Declaration of Helsinki.

Patient consent for publication

Patient consent was obtained from the parents of the infant described herein, and consent was also obtained for the publication of the present case report and any related images.

Competing interests

The authors declare that they have no competing interests.

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