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Caso Clínico

Continuous Glucosee Monitoring in Real Time in Premature Infant: A Challenge

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A B S T R A C T

Neonatal diabetes mellitus is a rare disorder defined as persistent treatment-requiring hyperglycemia during the first six months of life. Diagnosis and management can be challenging, especially in transient cases. We present a case of an extremely low birth weight premature infant with transient neonatal diabetes mellitus. In the first days of life he developed persistent hyperglycemia requiring the need to start an insulin infusion. It was difficult to adjust insulin doses due to the small quantities with variable requirements, so real-time continuous glucose monitoring was initiated. This system showed a good correlation with capillary glycemia, allowing adjustments of insulin perfusion and consequently normalizing the infant's blood glucose levels. This report highlights the usefulness of real-time continuous glucose monitoring for monitoring insulin therapy in patients with transient neonatal diabetes mellitus, particularly in those with comorbidities as in this case.

Keywords:
Blood Glucose;
Hyperglycemia;
Infant, Newborn;
Infant, Premature;
Monitoring, Physiologic.

Monitorização Contínua da Glicose em Tempo Real no Prematuro: Um Desafio

R E S U M O

A diabetes *mellitus* neonatal é uma entidade rara definida como uma hiperglicémia persistente que requer tratamento e ocorre nos primeiros seis meses de vida. O diagnóstico e o tratamento podem ser desafiantes, principalmente nos casos transitórios. Apresentamos o caso de um prematuro de extremo baixo peso com diabetes *mellitus* neonatal. Nos primeiros dias de vida apresentou hiperglicemia persistente com necessidade de iniciar uma perfusão de insulina. Foi difícil de ajustar as doses de insulina devido às pequenas quantidades e necessidades variáveis, por isso foi iniciada a monitorização contínua da glicose em tempo real. Este sistema mostrou uma boa correlação com a glicémia capilar permitindo uma ajuste da perfusão de insulina e consequente normalização da glicémia. Este caso clínico destaca a utilidade da monitorização contínua da glicose em tempo real para monitorizar a insulinoterapia em pacientes com diabetes *mellitus* neonatal, principalmente naqueles com comorbilidades como o caso apresentado.

Palavras-chave:
Glicemia;
Hiperglicemia;
Monitorização Fisiológica;
Recém-Nascido;
Recém-Nascido Prematuro.

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Introduction

Hyperglycemia is a symptom present in some neonates, especially in the preterm or low birth weight (LBW) infant. Typical causes for hyperglycemia in this group include an immature pancreas, increased parenteral glucose administration, infection, insulin resistance, increased counter-regulatory hormones due stress, and medications, such as steroids.[1] Additionally, neonatologists should consider neonatal diabetes mellitus (NDM), a rare condition where hyperglycemia is persistently greater than 250 mg/dL (13,88 mmol/L)[1] for longer than two weeks, in the absence of other predisposing factors.[2,3]

NDM is defined as persistent treatment-requiring hyperglycemia occurring in the first six months of life.[4,5] Its frequency varies between different populations, in Europe the incidence rate ranged between 1 in 90 000 and 1 in 500 000.[6,7] This condition can either be permanent neonatal diabetes mellitus (PNDM), requiring lifelong treatment, or transient neonatal diabetes mellitus (TNDM).[2,8] TNDM represents about 50% of NDM cases[5,9] and is biphasic: usually remit spontaneously within one to 18 months, but often recurs during adolescence or early adulthood.[7,8,10]

NDM is a heterogeneous disease predominantly monogenic.[11-13] It is recommended to perform a genetic test in infants with NDM because identifying the genetic cause has many clinical benefits: first, it can help to select the best treatment (some individuals with a specific mutation may be successfully treated with sulfonylureas); secondly, it can predict the development of some extrapancreatic features; finally, to provide genetic counselling to the family.[7]

Obtaining and maintaining a good glycemic control is important to prevent adverse neurological outcomes. But, the close monitoring, results in numerous blood glucose tests which can be technically demanding for caregivers and traumatic for infants.[14,15]

Therefore, the advent of real-time continuous glucose monitoring (RT-CGM) systems enables the optimization of metabolic control. RT-CGM consists of a small monitoring device that receives a signal by Bluetooth from a sensor inserted into the subcutaneous layer. The sensor using the glucose in the interstitial fluid, produces a small electrical current that is proportional to the glucose concentration. Calibration algorithms convert sensor signals into RT-CGM output (glucose value). Calibration blood sugar measurements are required to convert electrical current into meaningful RT-CGM output. After initial calibration, it is recommended that RT-CGM devices be calibrated two times a day.[16] Data are monitored and showed in real time on the monitor. RT-CGM (Paradigm™ Veo™, Medtronic MiniMed), an insulin pump enhanced with RT-CGM, was the device used to control the blood glucose level (BGL) in the case described.

This device provides information not only about the current interstitial glucose level but also glucose trends, which are important to anticipate therapeutic measures, when metabolic control is a challenge.

Clinical Case

In this report, we present a case of an extremely LBW infant with NDM.

At 24 weeks' gestation, a 21-year-old woman pregnant with twins was admitted to the hospital after threatened preterm labor. There was no maternal history of gestational diabetes or hypertension. Maternal serologic screening was negative and the prenatal ultrasounds were normal. Parents were nonconsanguineous and no history of diabetes in the family was reported. The mother received a complete cycle of antenatal corticosteroids and she delivered two infants at 25 weeks' gestation by cesarean section. The first twin did not survive. The second twin was a male with weight 765 g (<3rd centile), length 34 cm (<3rd centile) and head circumference 23 cm (<3rd centile), according to Fenton growth charts. He was intubated in the delivery room.

On the first day of life, the newborn was under mechanical ventilation and hemodynamically stable. Blood tests (arterial blood gas, blood count, C-reactive protein, glucose) were normal and he initiated antibiotic prophylaxis. On the second day of life, under parenteral nutrition with 5.9 mg/kg/min of glucose, he developed hyperglycemia with BGL persistently >300 mg/dL (16.65 mmol/L) despite a decrease in the glucose infusion rate of 3.1 mg/kg/min. After five boluses of insulin (0.05 units/kg/dose), the BGL remained high, >250 mg/dL (13.88 mmol/L), and according to our departmental protocol, the newborn started an insulin infusion with a dose 0.01 units/kg/hour. The dose was then adjusted to achieve normoglycemia (insulin infusion maximum dose was 0.01 units/kg/hour) and the BGL dropped down to <200 mg/dL (11.1 mmol/L). Insulin doses were reduced gradually and finally discontinued on day 16, when he was normoglycemic on full feeds (180 mL/kg/day of breast and premature milk).

On the 29th day of life he was extubated, after corticotherapy, and developed again hyperglycemia, >400 mg/dL (22.2 mmol/L). Laboratory results showed C-peptide level of 2.1 ng/mL (normal, 1-7.6 ng/mL), and insulin level of 3.7 uIU/mL (normal, <30 uIU/mL), further reflecting relative insulin deficiency (both drawn when the serum glucose level was 200 mg/dL (11.1 mmol/L). We restarted an insulin infusion with a dose of 0.009 units/kg/hour, (insulin

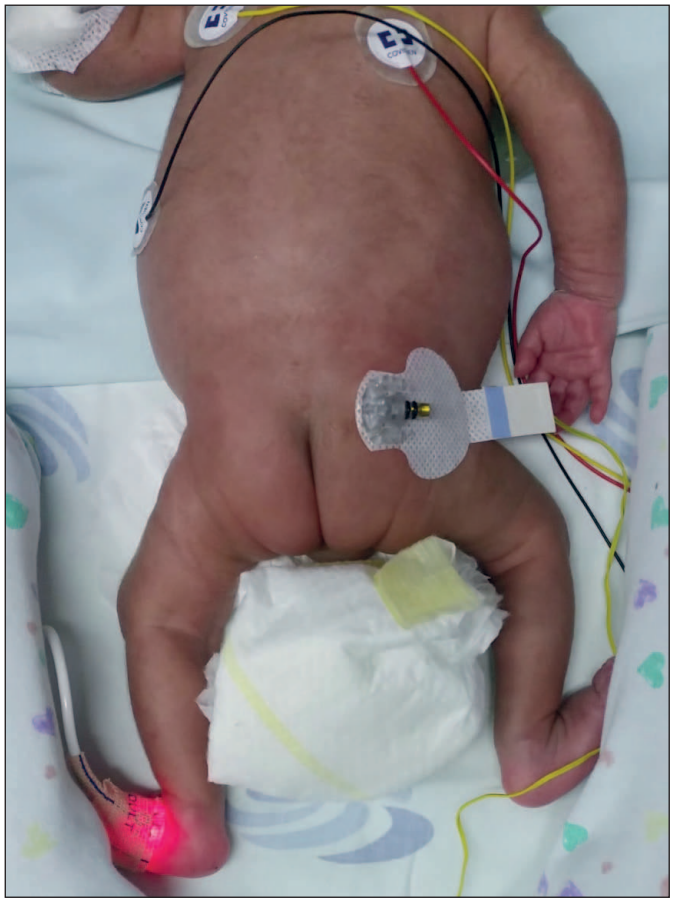

Figure 1. Real-time continuous glucose monitoring sensor inserted into the subcutaneous layer of the patient.

infusion maximum dose was 0.01 units/kg/hour) but this time with marked difficulty in dose due to the small quantities of insulin with variable requirements.

Pediatric endocrinologist suggested initiating RT-CGM at this time. The sensor was inserted into the subcutaneous layer in the upper buttock area (Fig. 1). We defined the target serum glucose levels between 70 mg/dL (3.9 mmol/L) and 140 mg/dL (7.8 mmol/L), being 50 mg/dL (2.8 mmol/L) the cut-off for hypoglycemia. Alarms for thresholds, >250 mg/dL (13.9 mmol/L) or <70 mg/dL (3.9 mmol/L) were introduced in the system. Due to minute doses of insulin required, 1:10 insulin dilution was necessary. Twice a day the nurse calibrated glucose measurements. The sensor was changed every seven days. Two weeks of continuous glucose monitoring trace (Fig. 2) showed fluctuations in interstitial glucose concentrations varying with the meals. We adjusted the insulin perfusion to this glucose profile. Initially, there was a needed to increase the insulin perfusion after the meal (for two hours), and decrease the insulin perfusion before the meal (one hour earlier). Then the insulin perfusion was suspended for one hour a day (before one meal in the afternoon). When the alarm was activated, a capillary blood sampling was performed to confirm the glycemia value: confirmed hypoglycemia led to stop insulin infusion temporarily and one hour later performed a new capillary blood sampling; confirmed hyperglycemia led to increasing the insulin infusion.

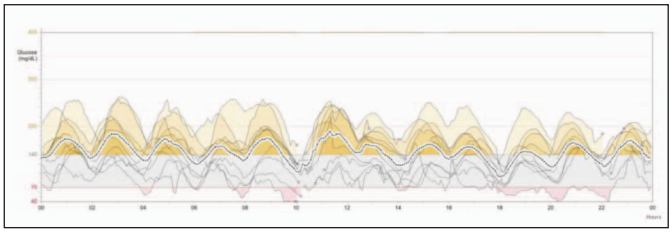

Figure 2. Two weeks continuous interstitial glucose monitoring trace. The mean glucose concentration was 144 ± 36 (standard deviation) mg/dL (7.9 ± 2 mmol/L)

The RT-CGM showed a strong correlation with capillary glycemia (correlation coefficient of 0.817) allowing adjustment of insulin perfusion with normalization of BGL (Fig. 3). During use of RT-CGM the mean of capillary BGL was 118±20 mg/dL (6.5±1.1 mmol/L) and the mean of sensor glucose levels was 126±18 mg/dL (6.9±1 mmol/L) , time in range was 78.1% of total, and time in hypoglycemia was 0.4% of total.

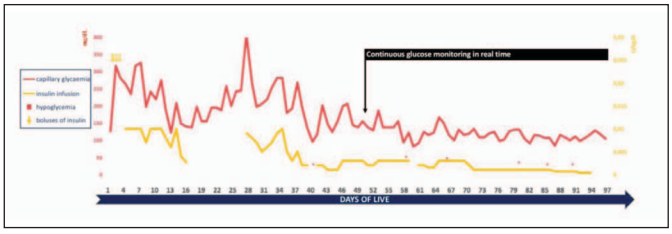

Figure 3. Evolution of capillary glycemia and insulin infusion of the patient. The red line represents the daily mean of capillary glycemia; the yellow line represents intravenous insulin infusion. The cutoff for hypoglycemia was 50 mg/dL (2.8 mmol/L)

This system allowed to reduce the number of daily capillary blood samples from eight to two, and no complications, such as bleeding, edema or local infection, were described. There was no severe hypoglycemia. Overall insulin requirement decreased, treatment was progressively reduced and stopped on day 95, with the infant remaining normoglycemic ever since, consistently with TNDM.

The infant was discharged home after a lengthy hospital stay due to other complications: a peri-intraventricular hemorrhage (PIVH) grade 3; late-onset *sepsis* (*Staphylococcus Haemolyticus*) treated with vancomycin; and he was also diagnosed with bilateral retinopathy of prematurity grade III.

On discharge, 117 days of live (five days corrected age), he was feeding well with normal BGL and showed a catch-up growth. He is followed by the pediatric endocrinology team and remains asymptomatic without treatment until now. The parents refused to perform the genetic test.

Discussion

Insulin plays a critical role in promoting growth in the fetus.[14] Patients with NDM are more likely to have intrauterine growth retardation because they have lower insulin levels during fetal life. According to Besser *et al*,[17] reduced birth weight in patients with NDM is well-described and prematurity can result from early elective delivery due to poor fetal growth. The patient presented a metabolic profile consistent with TNDM, which can justify his LBW and the associate prematurity.

PIVH was one of the prematurity-related complications present in the infant. In LBW infants hyperglycemia was associated with increased risk for PIVH grade 3-4.[18] However recent randomized trials did not show any benefit of continuous insulin infusion for PIVH in hyperglycemic preterm infants.[19,20] Other risk factors, such as LBW, low Apgar score, and postnatal complications have been associated with PIVH.[21] The PIVH present in our premature is probably due to these risk factors, but possibly persistent hyperglycemia in the first days of life also has a contribution.

Our case demonstrates the complex management of diabetes in an extremely preterm with associated comorbidities. At first, the diagnosis can be challenging because there are alternative causes of hyperglycemia in the preterm or LBW infant, in whom hyperglycemia occurs in 40%–80% in the neonatal intensive care unit.[22] Secondly, insulin therapy in these infants can be problematic, as they require ultra-small doses to cover the small carbohydrate intake, meaning that insulin dilution may be necessary and that is technically difficult and associated with an increased risk of error.[11] Due to the paucity of subcutaneous fat and muscles in these tiny LBW newborns, regular insulin is routinely used intravenously, which usually leads to the dilemma of either hypoglycemia or hyperglycemia again after stopping insulin, as happened in our case.[23] Furthermore, in these infants, the increased need for some medications or the highest risk of infections contributes even more to the fluctuation of BGL. We faced this situation after stopping insulin infusion, due to hypoglycemia episodes. The patient gradually developed hyperglycemia, which was exacerbated by corticotherapy, requiring the need to initiate insulin infusion again. Galal *et al*[23] faced the same frustrating cycle of hyperglycemia followed by hypoglycemia and vice-versa. Finally, the need for monitoring the BGL requires repeated blood draws or manipulation of central lines which should be avoided to reduce the risk of infections and anemia.[24,25]

As described above, managing LBW with NDM presents many problems, therefore achieving a metabolic control and also avoiding potentially dangerous hypoglycemic events can be very difficult. In the patient, when the glycemic control became very difficult to achieve with a consequent need of frequent invasive blood sampling, we started to use the RT-CGM device. Its use in infants is off-label, being only approved in children older than 4 years with type 1 diabetes.[26] Due to this, some aspects should be carefully considered for its use in the neonatal population. For instance RT-CGM devices

use algorithms based on interstitial glucose–blood glucose kinetics in adults, which have not been tested specifically or rigorously in neonates.[27] An important limitation of the RT-CGM instrument is to provide measurements of glucose only in a large range and preterm infants require accuracy for management of glucose concentrations. Still, some studies conclude that using RT-CGM is safe and reliable in preterm infants.[24] They also demonstrated that glucose results correlate well with BGL with minimal bias,[28] so its use (even off-label) is very important to make therapeutic decisions.

RT-CGM devices use a fine needle sensor inserted into the subcutaneous tissue. Unlike the subcutaneous administration of rapid acting insulin that has to be administered several times per day, the sensor inserted into the subcutaneous tissue is changed every seven days. Furthermore the minute doses of insulin required to make the subcutaneous administration of insulin are even more difficult. Therefore in our neonate intravenous insulin infusion was preferred. Currently, there are available RT-CGM systems integrated with continuous subcutaneous insulin pumps. They have an automated algorithm-driven insulin dosing that liberates the patient/caregiver from managing insulin therapy.[29] It is an available option if the patient requires a long insulin-treatment and his weight is appropriated to an adequate insulin dose.

Despite off-labell use, the application of the sensor appeared to be safe and well tolerated as established by Beardsall *et al*.[28] Other two studies[24,30] also reported that needle sensors were well tolerated, even in infants weighing <1500 g. The lowest birth weight reported in these two studies[24,30] was 579 g. There have been no reports of local complications, such as infection, edema, bleeding or bruising.[31]

The interstitial subcutaneous glucose concentration mirrors the BGL, reflecting even more rapid changes.[15] Consequently, RT-CGM devices provide information about the current interstitial glucose level and glucose trends,[26] allowing the adjustment of insulin. The use of RT-CGM in LBW infants has the potential to minimize the incidence and severity of hypoglycemia and hyperglycemia with a non-invasive monitoring of glucose profiles, improving glucose stability by adjusting its intake and insulin perfusion in real-time according to individual metabolic requirements.[27,31] Uettwiller *et al*[30] compared RT-CGM with intermittent blood glucose monitoring in very LBW infants and found that RT-CGM reduced the median duration of hypoglycemic episodes by 50% and the number of capillary blood samples by 25%. This was attributed primarily to earlier detection of episodes by RT-CGM more than by regular intermittent capillary blood glucose testing.[31]

The infant presented a metabolic profile consistent with TNDM, which is mainly caused by mutations in the genes *KCNJ11* and *ABCC8*.[13] Mutations in these genes may be treated with oral sulfonylureas, instead of subcutaneous insulin, improving glycemic control and increasing the quality of life.[1] Since TNDM often recurs during adolescence or early adulthood, a genetic cause identified could orientate the treatment in the future.

RT-CGM was crucial achieving euglycemia in the infant, allowing clinicians to keep glucose concentrations within a narrower range, and no complications were reported. This newborn was the smallest premature with NDM managed with RT-CGM described in our country.

Responsabilidades Éticas

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