Hiperglucemia neonatal en un recién nacido prematuro manejado con una bomba de insulina subcutánea.

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SUMARIO:

PROPÓSITO:

Se describe el uso exitoso de una bomba de insulina subcutánea para administrar insulina regular a un bebé prematuro con hiperglucemia neonatal.

RESUMEN:

Se observó que un bebé femenino de 520 g nacido a las 23 semanas de edad gestacional a través de una cesárea tenía concentraciones elevadas de glucosa en sangre de hasta 180 mg / dL (en unidades SI, 10 mmol / L) el día de la vida (DOL) 3 y alcanzar el máximo en DOL 9 a 250 mg / dL (13,9 mmol / L) a pesar de las tasas conservadoras de infusión de glucosa. La infusión continua de insulina regular se inició en DOL 8 y continuó a través de DOL 44, con una tasa promedio de infusión de insulina de 0.08 unidades / kg / h. El paciente experimentó labilidad de la concentración de glucosa en sangre debido a múltiples factores, lo que resultó en la necesidad de un monitoreo frecuente y rutinario de la concentración de glucosa en sangre para minimizar los eventos de hipoglucemia. En DOL 44, se colocó una bomba de insulina subcutánea y se usó para proporcionar insulina regular diluida (25 unidades / ml). Después de 1 semana, la concentración de glucosa en sangre del paciente se normalizó, lo que condujo a una reducción en la frecuencia de monitoreo de glucosa. Después de 3 semanas, se suspendió el uso de la bomba de insulina. El paciente permaneció euglucémico a partir de entonces.

CONCLUSIÓN: El uso de una bomba de insulina resultó en una disminución de los controles de glucosa en sangre, la interrupción del acceso a la línea central y, en general, una mejor atención al paciente.

Neonatal hyperglycemia in a preterm infant managed with a subcutaneous insulin pump

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Purpose. Successful use of a subcutaneous insulin pump to administer regular insulin to a preterm infant with neonatal hyperglycemia is described.

Summary. A 520-g female infant born at 23 weeks' gestational age via caesarian section was noted to have elevated blood glucose concentrations ranging up to 180 mg/dL (in SI units, 10 mmol/L) on day of life (DOL) 3 and peaking on DOL 9 at 250 mg/dL (13.9 mmol/L) despite conservative glucose infusion rates. Continuous infusion of regular insulin was begun on DOL 8 and continued through DOL 44, with an average insulin infusion rate of 0.08 units/kg/h. The patient experienced blood glucose concentration lability due to multiple factors, resulting in the need for frequent and routine blood glucose concentration monitoring to minimize hypoglycemia events. On DOL 44, a subcutaneous insulin pump was placed and used to provide diluted regular insulin (25 units/mL). After 1 week, the patient's blood glucose concentration normalized, which led to a reduction in the frequency of glucose monitoring. After 3 weeks, insulin pump use was discontinued. The patient remained euglycemic thereafter.

Conclusion. The use of an insulin pump resulted in decreased blood glucose checks, discontinuation of central line access, and overall better patient care.

Keywords: diluted regular insulin, extremely low-birthweight neonate, neonatal hyperglycemia, subcutaneous insulin pump

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Hyperglycemia in preterm neonates is not an uncommon phenomenon due to immaturity of the vital organs. However, neonatal diabetes mellitus, both transient and permanent, is a rare finding, occurring in approximately 1 in every 90,000 to 160,000 live births.[1,2] Diagnostic criteria for neonatal diabetes include documented hyperglycemia for more than 2 weeks during the first 6 weeks to 6 months of life requiring management with insulin therapy.[3,4] The definition of neonatal hyperglycemia may differ in a preterm neonate as opposed to a term neonate.[5] Although half of all patients with neonatal diabetes mellitus will have transient disease, which resolves by 18 months of life, these patients are at risk for relapse and have an increased risk of developing type 2 diabetes later in life.[1,3] Patients with permanent neonatal diabetes mellitus will continue to require insulin therapy as they continue to grow and develop.[4]

Continuous intravenous (i.v.) insulin infusions, subcutaneous insulin injections, and sulfonylurea therapy are among the few treatment options available for neonatal diabetes and neonatal hyperglycemia.[2,6] These approaches pose significant clinical challenges, particularly in the care of preterm infants, for whom evidence-based treatment approaches are limited due to minimal research data and restricted availability of insulin products in concentrations suitable for extremely low-birthweight infants.[2,4] In the case described here, insulin glargine was discussed as a

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possible option; however, its use would have required dilution to administer an appropriate dose, and due to significant variation in the patient's blood glucose concentrations, the team was concerned about using a long-acting insulin product.

Case report

The patient was a female newborn with a gestational age of 23 weeks and 2 days. The pregnancy was significant for a maternal history of asthma, a 2-vessel cord, and premature rupture of membranes 6 days prior to delivery. Antenatal steroids were administered prior to delivery. Birth anthropometric measurements were as follows: weight, 520 g (*z* score, –0.42 per the Fenton 2013 Growth Calculator [copyright, Joseph Chou]); length, 26.5 cm (*z* score, –1.58); and head circumference, 18 cm (*z* score, –2.29). The patient's initial Apgar scores were 1 at 1 minute of life and 2 at 5 minutes of life.

On day of life (DOL) 3, the patient began experiencing hyperglycemia, with blood glucose concentrations of 180 mg/dL (in SI units, 10 mmol/L) despite a glucose infusion rate (GIR) of 4.2 mg/kg/min. By DOL 8, the patient continued to have sustained blood glucose concentrations greater than 190 mg/dL (10.5 mmol/L) despite a decreased GIR (3.6 mg/kg/min). The decision was made to start a continuous i.v. infusion of regular insulin (0.25 unit/mL in 0.9% sodium chloride) at a rate of 0.02 units/kg/h. On DOL 9, blood glucose concentrations increased to 250 mg/dL (13.9 mmol/L) despite continuous i.v. administration of regular insulin, infused at a rate of 0.12 units/kg/h, and a GIR of 4.1 mg/kg/min (Figure 1).

Despite the use of properly primed tubing for continuous i.v. infusion of diluted regular insulin, the patient experienced significant lability of serum and blood glucose concentrations, necessitating blood glucose checks via heel poke every 1 to 2 hours. (While one may hypothesize that the insulin was degrading over time, we did not conduct a degradation analysis on the insulin i.v. bags.) Concentration lability was noted throughout the entire 24-hour period of the infusion. On DOL 24, the patient was started on dexamethasone for 3 days. An additional 10-day course of dexamethasone was initiated on DOL 35. Both of these dexamethasone courses, used to facilitate extubation, resulted in increased blood glucose concentrations. Additionally, the patient was accepting full feeds at DOL 26 yet still needed a central line and additional fluid to provide continuous i.v. insulin. In subsequent days the patient required 12 to 23 blood glucose concentration determinations daily. Monitoring was hourly if readings were outside the range of 80 to 150 mg/dL (4.4-8.3 mmol/L). If 3 consecutive glucose concentrations were within the desired range, monitoring was spaced at every 2 hours; if 3 additional glucose concentrations were within range, monitoring was spaced at every 3 hours.

On DOL 44, the patient weighed 780 g and was receiving enteral feeds of fortified maternal breastmilk over 3 hours followed by a 1-hour break from feeding. Blood glucose concentrations were still variable (Figure 2). The team discussed with the patient's mother risks vs benefits of treatment options, including continuation of the insulin infusion, and maternal consent to proceed with use of a subcutaneous insulin pump to control the patient's blood glucose concentrations was given.

The team used a Medtronic 630G insulin pump with a 13-mm Silhouette infusion set (Medtronic, Minneapolis, MN) affixed with a Mepilex dressing (Mölnlycke Health Care AB, Gothenburg, Sweden) to a buttock. That particular insulin pump allows for dosage adjustments in increments of 0.025 unit/h with use of insulin 100 units/mL. Due to the size of the patient, the pump reservoir was filled with regular insulin diluted with 0.9% sodium chloride to a final concentration of 25 units/mL. With the use of diluted insulin, the dosage adjustments were reduced to 0.00625 unit/h. The reservoir was prepared and allowed to sit refrigerated at least 6 hours prior to administration to allow the insulin to bind to the tubing and the reservoir, thereby providing the patient with a consistent concentration of infused insulin. The reservoir and tubing were changed daily, and the application site was rotated every 3 days. The device was kept outside of the incubator to minimize degradation of the insulin by the warmth of the incubator.

To ensure safe administration of the diluted regular insulin to the patient, the team provided education to nursing and pharmacy personnel, providers, and the mother of the patient. The pump was unable to recognize that diluted insulin was being placed in the reservoir; therefore, in the electronic medical record we edited insulin orders to stipulate patient-specific doses to prevent confusion. Specifically, we noted that for the purposes of pump programming (1) a bolus of 0.25 unit of diluted insulin was equivalent to 1 unit and (2) a basal rate of 25 units/h of diluted insulin was equivalent to 100 units/h. For this patient, we made notations in multiple places, including on the medication order, the label,

KEY POINTS

- A subcutaneous insulin pump was successfully used to administer diluted regular insulin to an infant who weighed less than 1 kg.
- The frequency of point-of-care blood glucose concentration monitoring was decreased with the implementation of the subcutaneous insulin pump.
- This approach may be an option for other practitioners working with neonates who accept full feeds yet continue to have hyperglycemia and require insulin therapy, and it may allow for discontinuation of intravenous access.

Figure 1. Macronutrients provided to the neonate in parenteral nutrition in relation to maximum and minimum blood glucose levels. The patient received maternal breastmilk trophic feeds (4-12 mL/kg/d from days of life 3 to 7, 40 mL/kg/d from days of life 8 to 10, and 65 mL/kg/d on days of life 11 and 12).

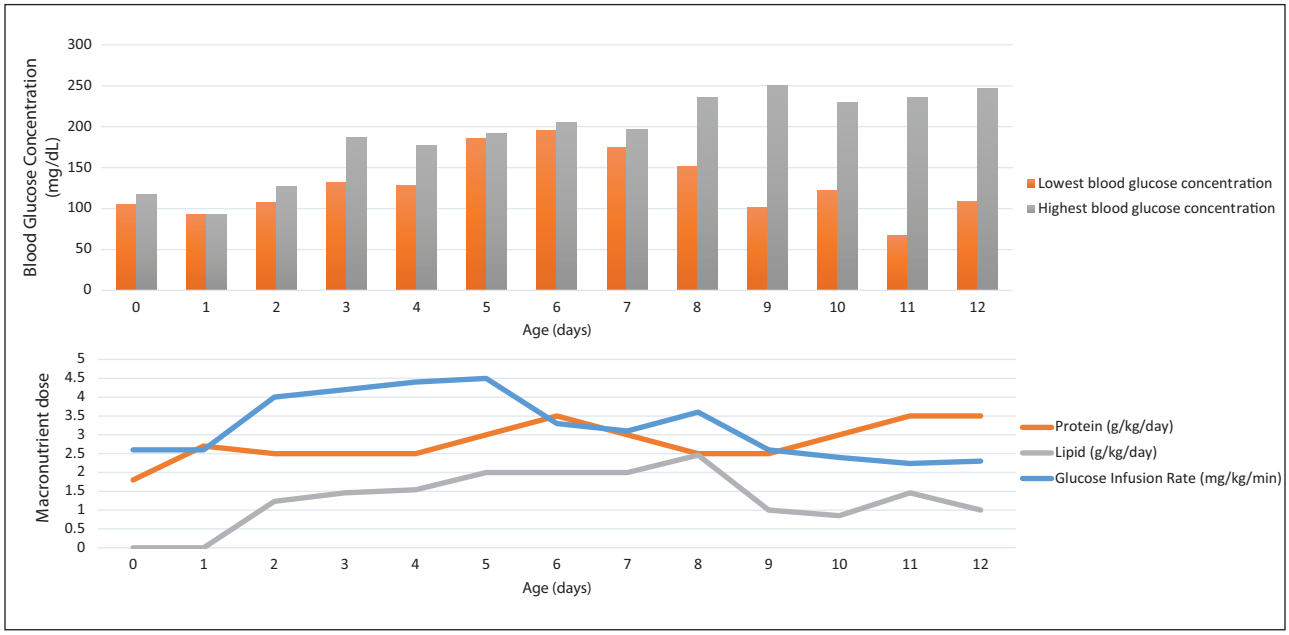
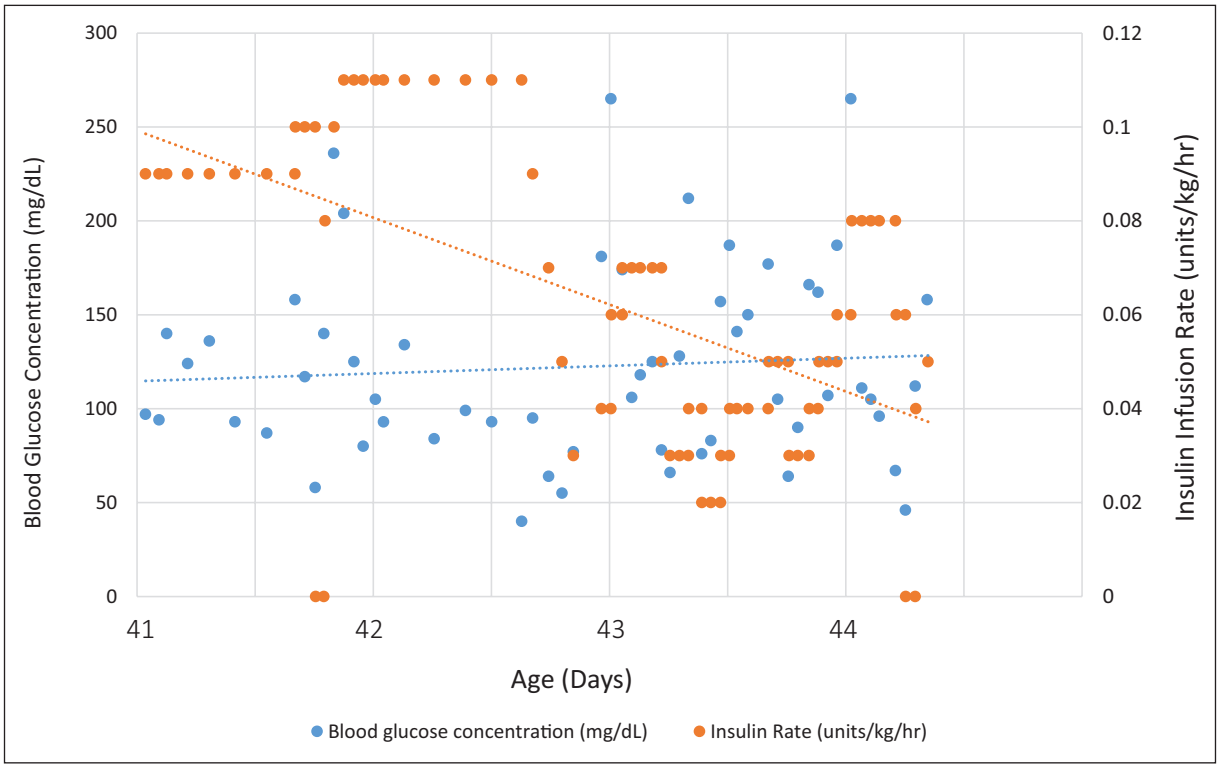


Figure 2. Continuous insulin infusion dosing and blood glucose levels prior to initiation of subcutaneous insulin pump use. The dotted lines show trends.



and a patient note, stating, "0.025 unit/h on the insulin pump is equivalent to 0.00625 unit/h when filled with diluted regular insulin 25 units/mL." Additionally, we engaged designated staff, including specific pharmacy technicians, pharmacists, nurses, and providers, to help decrease the chance of error.

The team decided to start insulin therapy at the lowest rate possible. The pump was started at a rate of 0.00625 units/h (0.008 unit/kg/h), with instructions to nursing staff to suspend the pump in the event of blood glucose concentrations of <80 mg/dL (4.4 mmol/L). Glucose levels were monitored hourly. During the first 48 hours, there were occasional episodes of hypoglycemia despite this reduced insulin rate. Therefore, subcutaneous diluted regular insulin therapy was modified to a schedule of 0.00625 units/h "on" for 2 hours followed by 2 hours "off." The start of each infusion cycle coincided with the start of enteral feeds. After the first 48 hours, blood glucose concentrations stabilized, and at the 72-hour mark, assessments of blood glucose concentrations were spaced every 2 hours. On day 5 of implementation (DOL 49), blood glucose concentrations were spaced every 4 hours and evaluated just prior to the feed. There were no notable decreases in blood glucose levels with daily changes of the reservoir.

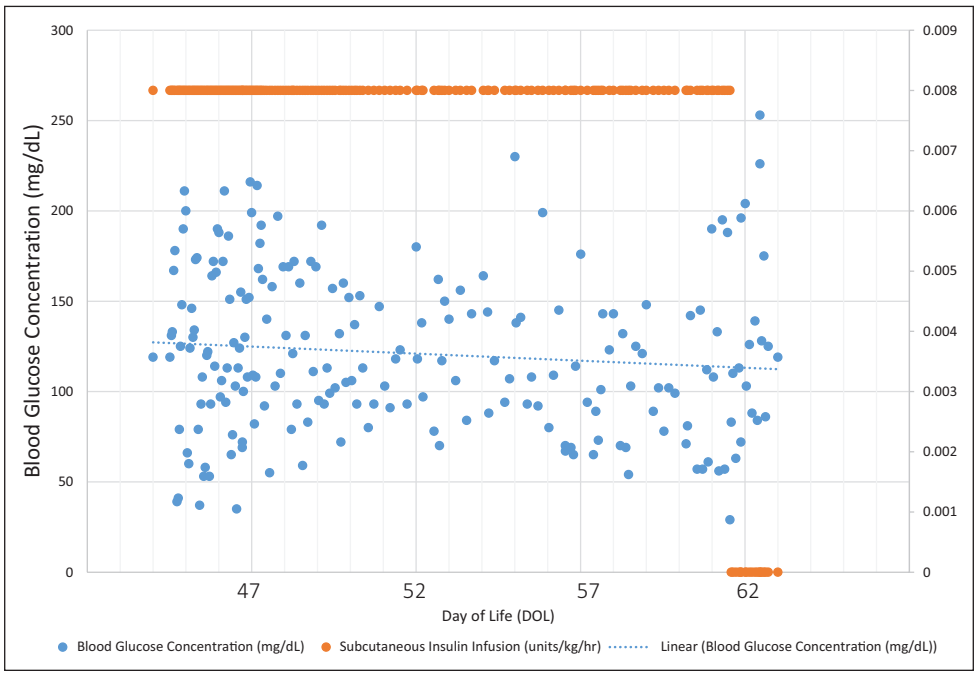
From DOL 46 to DOL 60 the patient remained stable on the 2 hours on, 2 hours off insulin infusion regimen (Figure 3). As a result, monitoring of blood glucose concentrations was decreased from every 1 to 2 hours to every 4 to 6 hours. The patient experienced a single episode of hypoglycemia on DOL 60, at which time use of the insulin pump was discontinued. Hypoglycemia did not reoccur, and hyperglycemia did not occur. The infant was discharged on DOL 121 at a corrected gestational age of 40 weeks and 4 days. Anthropometric measurements at discharge were as follows: weight, 2.749 kg (z score, –1.64); length, 43 cm (z score, –3.55); and head circumference, 33 cm (z score, –1.46).

Genetic evaluation for known mutations associated with transient and permanent neonatal diabetes responsive to sulfonylurea therapy was performed, and the results were negative. Not all genetic variants associated with transient and permanent neonatal diabetes were evaluated, and therefore transient neonatal diabetes cannot be ruled out. Additionally, a serum insulin concentration and C-peptide concentration, which could have aided in the determination of neonatal hyperglycemia vs transient neonatal diabetes, were not obtained for this patient. In the future, if we were to encounter this type of patient again, we will utilize these markers to provide a more complete picture and assessment of the patient.

Discussion

Although insulin therapy for neonatal diabetes is a common practice, the optimal strategy for management of these patients is not clearly defined in the current medical literature.[7] The use of insulin pumps in neonatal diabetes

Figure 3. Blood glucose concentrations after initiation of subcutaneous insulin pump use. The insulin infusion continuously ran at 0.008 units/kg/h (2 hours on, 2 hours off) on days of life 47 to 60. On day of life 60, pump use was discontinued (note insulin rate value of 0).



mellitus is documented in a handful of cases in the literature. However, many of these cases involved infants at or near term gestation and did not highlight the challenges of insulin administration to tiny infants.[2,8-11] To date, no cases involving the use of a subcutaneous insulin pump in a neonate weighing less than 1 kg have been published. None of the published cases involved use of diluted regular insulin.

It is important to note that the use of the aforementioned insulin pump for neonatal diabetes constitutes an off-label use, and administration of regular insulin in the circumstances described is also an off-label use. It is vital when considering implementation of this type of device to administer regular insulin (diluted or not) that clear instructions are provided to the medical team and to caregivers if this treatment is provided in an outpatient setting. Additionally, there is currently no subcutaneous insulin pump available to allow programming of diluted insulin to reflect the proper units. The use of diluted insulin in an insulin pump intended for undiluted insulin represents a safety risk, which should be weighed carefully against the benefits of such a practice.

In the pharmacy, the diluted regular insulin (25 units/mL) was prepared for the patient using insulin and 0.9% sodium chloride. Reservoirs for the insulin pump were filled ahead of time with the diluted insulin and allowed to sit for at least 6 hours prior to being placed in the subcutaneous pump for administration to the patient to help minimize variability in concentration due to insulin leaching into the reservoir and tubing. Implementation of subcutaneous insulin therapy involved a multidisciplinary team including pediatric endocrinology, neonatology, nursing, and pharmacy personnel. Once the patient was started on the insulin pump, we achieved stable blood glucose concentrations and were able to improve the patient's quality of life by decreasing the frequency of point-of-care glucose monitoring. Additionally, there were less fluctuations in the patient's insulin requirements, less manipulation of insulin rates, and less insulin was required overall. The decrease in insulin requirements may have been due to less insulin binding to the tubing during the administration process with the subcutaneous insulin pump, or could have been due to the patient getting older and outgrowing transient neonatal diabetes.[12]

While the patient's initiation on the insulin pump decreased the number of low blood glucose concentrations, the variability seen before and after implementation were similar, as shown in Figures 2 and 3. The main advantages of using the subcutaneous pump were that it allowed for discontinuing central i.v. access, minimizing changes to the insulin infusion regimen to prevent hypoglycemia and hyperglycemia, and programming an insulin infusion regimen that easily followed the patient's enteral feeds. Additionally, the patient had decreased numbers of blood glucose measurements. Just prior to implementation she had required point-of-care blood glucose monitoring 12 to 23 times a day; after the first 4 days of insulin therapy with the subcutaneous pump, blood glucose monitoring was spaced to 6 times a day and performed just prior to feeds.

Conclusion

Although there is limited medical literature addressing the use of a subcutaneous insulin pump in extremely low-birthweight infants with neonatal diabetes, this case highlights a successful implementation of that form of insulin therapy. Subcutaneous insulin pumps may play a role in infants requiring insulin therapy who have significant fluctuations in insulin requirements or who continue to require insulin after parenteral nutrition is no longer required. A multidisciplinary approach including input from primary providers and nursing, endocrinology, and pharmacy personnel along with excellent documentation and communication was key for safe and successful treatment.

Disclosures

The authors have declared no potential conflicts of interest.

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