Safety and accuracy of neonatal continuous glucose monitoring

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Safety and Accuracy of Neonatal Continuous Glucose Monitoring

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SAFETY AND ACCURACY OF NEONATAL CGM

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Abstract

Background

Hypoglycemia is a significant problem for all neonates and requires minimally invasive and reliable monitoring. The primary objective of this study is to verify the safety and accuracy of continuous glucose monitoring (CGM) of full-term neonates using Freestyle® Libre, a flash glucose monitoring (FGM) device.

Methods

The study was conducted on twenty neonates. Shortly after birth, we placed the FGM sensor on the outside of the neonates' thighs. We scanned the CGM values at 60, 120, 180 and 360 min after birth and simultaneously obtained blood glucose values with plantar capillaries by heel puncture. The neonates wore the sensors for up to 6 hours and then they were removed.

Results

Out of the 75 data points to be measured, 65 points (86.7%) were obtained by scan. There was no change in the sensor attachment site in 12 of 18 completed cases in this study, but we observed slight induration in 4 cases (22.2%) and slight redness in 1 case (5.5%) at the sensor puncture site. A moderate correlation was observed between the CGM and blood glucose values. The CGM values tended to be low at 120, 180, and 360

min after birth, and tended to be high only at 60 min after birth.

Conclusions

The CGM device was safe to wear on the neonate, and the CGM data correlated well with blood glucose levels. There is dissociation between CGM data and blood glucose levels in the acute period soon after birth when the blood glucose levels change rapidly.

Key words

Accuracy, Blood glucose, Neonate, Safety, Continuous glucose monitoring

Introduction

All neonates have transient hypoglycemia due to the disruption of the placental glucose supply after birth. The same is true for full-term neonates, but it is known that when insulin secretion is suppressed, gluconeogenesis and lipid decomposition start, and the lowered blood glucose level naturally rises. Therefore, current guidance recommends glucose monitoring for at-risk neonates and does not recommend this in all non-at-risk neonates [1)]. However, hypoglycemia causes severe irreversible brain damage in all neonates resulting in a poor neurological outcome [2)].

Although point-to-point blood glucose monitoring with frequent blood draws can reduce the chance of missing abnormal blood glucose levels, it is a painful and invasive procedure for neonates. Indeed, it has been reported that painful stimuli in the neonatal period affect neurological development [3)]. Furthermore, frequent measurements are cumbersome and time-consuming for physicians, and frequent interventions have the opposite effect to infection control.

A continuous blood glucose monitoring device, the Freestyle® Libre (Abbott Diabetes Care, CA, USA) is widely used for diabetic children; however, it is not approved for neonates. Thus, the primary object of this study is to verify the safety and accuracy of Freestyle® Libre attached to full-term neonates for the ultimate purpose of

introducing it to high-risk neonates.

Methods

This prospective, single-arm, clinical study was conducted at a single institute: the Maternal-Fetal Neonatal Center, Hamamatsu University Hospital, Shizuoka, Japan, between April 2018 and March 2022. The protocol and informed consent forms were approved as a specified clinical study by the Hamamatsu University School of Medicine Clinical Research Review Committee (approval number: C17-301, approval date: 18 January 2018) and registered with the Japan Registry of Clinical Trials (registered number: jRCTs042180045). All subjects' mothers provided written informed consent before labor began. The research was conducted in accordance with the World Medical Association's Declaration of Helsinki.

The study was conducted on twenty neonates. Since this research involved invasiveness in neonates, we gave detailed explanations (Purpose, Method and Predicted Disadvantages: pain, risk of infection and bleeding), and obtained informed consent before birth. We did not approach pregnant women who were particularly anxious about childbirth or who had comorbidities or pre-existing mental illnesses. In some cases, although consent was obtained, the study could not be conducted due to

the rapid progress of vaginal delivery or the lack of time to call the researcher.

The research subjects are neonates born between 37-0 and 41-6 weeks of gestation with no complications. Neonates born to mothers with diabetes, neonates with prenatal diagnosis of congenital anomalies, neonates admitted to the neonatal intensive care unit due to premature birth (<37+0 weeks) or respiratory complications and neonates deemed ineligible by the physician were excluded.

The FGM device

Freestyle® Libre is a 2017 FDA-approved factory calibrated flash glucose monitoring (FGM) device consisting of a small sensor that attaches to the skin and a handheld wireless reader that reads data wirelessly [4]. A thin electrode coated with an enzyme that reacts with glucose is placed under the skin, and the glucose concentration in the subcutaneous interstitial fluid is measured by amperometry. Data are recorded every 15 min for 8 hours in a measurement range of 40-500 mg/dL. The sensor body has a diameter of 35 mm, thickness of 5 mm, weight of 5 g, and a sensor electrode length of 4 mm.

Since the Freestyle® Libre is factory calibrated, there is no need for blood sampling; this may be less invasive to the neonate. In addition, it is possible to assess

the interstitial fluid glucose level in real time, which can be immediately used for therapeutic intervention. Furthermore, the history of blood glucose levels up to 8 hours can be viewed so unnoticed abnormalities can be identified. Since the sensor body is small, even if it is difficult to wear it on the arm of a small body, it can be worn on the outside of the thigh, which has a flat surface. The contactless readout is less likely to cause horizontal contact infection, making it suitable for use on neonates in the neonatal intensive care unit (NICU). However, Freestyle® Libre is intended for use in children aged four and up and is not approved for use in neonates or infants in Japan.

Although flash glucose monitoring and continuous glucose monitoring are strictly different, both allow glucose levels to be obtained continuously and timely with minimal invasiveness. The data obtained with the Freestyle® Libre in this study will be referred to as CGM scan data or CGM value below.

The CGM scan and blood glucose measurement

Shortly after birth, we placed Freestyle® Libre sensors to obtain continuous glucose monitoring data on the outside of the neonates' thighs using the attached applicator, after confirming that the neonate was breathing well and did not require NICU care. We performed sensor placement between 5 and 15 min after birth and

activated the scanning immediately. We scanned the CGM values at 60, 120, 180 and 360 min after birth. At the same time, we obtained blood glucose values with plantar capillaries by heel puncture. The time difference between the CGM scan and heel puncture data was within 1 min. We used OneTouch VerioVue® (LifeScan, PA, USA) range of measurement: 20-600 mg/dL for the measurement of blood glucose concentration, which is routinely used in our NICU and is believed to be accurate in measuring high hematocrit blood in neonates.

Freestyle® Libre can originally measure continuously for 14 days but since the effects of long-term sensor attachment on neonate skin are unknown, we decided to apply the sensor for up to 6 hours then remove it after scanning 360 min after birth. The condition of the skin where the sensor was applied was carefully observed for up to 24 hours after birth.

Statistical analysis

The statistical analysis was conducted using SPSS® statistics 27 (IBM, USA). The correlation between the glucose level measured from blood sampling and that from the Freestyle® Libre were analyzed using Pearson's product-moment correlation and linear regression. The differences between blood glucose and the CGM values were

analyzed using Bland-Altman analysis. Clarke error grid was used to evaluate the accuracy of the CGM values [5]. The differences between blood glucose and the CGM values for each measurement time or background factors were analyzed using Wilcoxon signed-ranks test. Comparisons between two groups were assessed with the Mann-Whitney U test. A p-value of less than 0.05 was considered statistically significant.

Results

A summary of the cases studied is shown in the Table 1. Twenty patients were fitted with Freestyle® Libre. There were 2 cases that we speculated that the sensor electrodes were not attached correctly: a case where 'LO' was displayed twice and then 'ERR' was displayed twice even though the blood glucose level was between 51 and 91 mg/dL, and a case where the 'ERR' was displayed and the numerical value was not displayed after that.

Eighteen cases had the sensor electrodes attached properly and scanning was started, but two patients dropped out of the study: one patient developed respiratory distress and one patient had hypoglycemia (blood glucose 38 mg/dL at 120 min), and both were admitted to the NICU. None of these events were determined to be related

to wearing of the Freestyle® Libre. Due to the discontinuation, it became impossible to measure all 5 data points, but the 3 data points obtained before study discontinuation of these two cases were used for analysis. There were also 2 points from other cases in which CGM data were not available with an “ERR” indication.

Out of the 67 scanned points, 7 points were marked as 'LO', which means “low glucose level” was also found when the CGM values were below the measurable limit. There does not seem to be a clear rule about how to handle values below the measurement limit; however, there is a method of tentatively substituting values below the lower limit of measurement for consideration. We substituted 39 mg/dL, as the Freestyle® Libre measurement limit is 40 mg/dL.

The scanning success rate was 80.6%; when ‘LO’ was also considered as successful, the success rate was 90.3% (Figure 1).

Safety

Changes in attachment sites were observed until 24 hours after birth. In 12 of 18 completed cases, there was no change in the sensor attachment site. We observed slight induration at the sensor puncture site in 4 cases (22.2%), slight redness in 1 case (5.5%), and purpura at the sensor detachment site in 1 case (5.5%). Induration and

redness disappeared by 2 days of age. In cases of observed purpura, we attempted to confirm if there was additional coagulopathy from blood drawing. In some cases, there was bleeding from the central puncture site. Bleeding stopped without persistence, so the study continued. No adverse events as sequelae were observed in any case.

Accuracy

We examined a total of 65 data points for which both the CGM and blood glucose values were obtained for statistical accuracy. A moderate positive correlation was observed between the CGM and blood glucose values (Pearson correlation coefficient $R=0.664$, $p<0.01$).

Bland-Altman analysis showed that the plot varies randomly within the limits of agreement (LOA) range, and it seems that the CGM and blood glucose levels are highly consistent with each other (Figure 2). There was no individual error (95% confidence interval -5.52 to 0.72). In addition, no fixed or proportional errors were observed ($p=0.998$). One point above the LOA was data at 180 min after birth, and two points below the LOA were at 180 and 360 min after birth. All of these are data from different sensors (cases) and we judged them to be random errors.

The Clarke error grid showed that there is moderate correlation between the

CGM and blood glucose levels (Figure 3). The percentages of results in Zones A and B were 84.6% and 13.8%, respectively. There was only 1 potentially dangerous measuring point (Zone D), which was data at 180 min after birth. The differences between the CGM and blood glucose levels were within 20% in 43 of 65 cases (66.1%).

We determined the mean absolute relative difference (MARD) every hour. MARD was 18.9 +/- 21.9, 18.4 +/- 9.6, 15.8 +/- 12.6, 15.9 +/- 7.5 at 60, 120, 180 and 360 min, respectively. Comparisons of these early measurement times within 6 hours of application showed no significant differences in MARD.

To clarify the factors of dissociation at each measurement time, the CGM and blood glucose values were compared (Figure 4). The CGM values tended to be low at 120, 180, and 360 min after birth and high only at 60 min after birth.

Discussion

There are existing reports of continuous glucose monitoring devices used for neonates. In Japan, only a few cases have been reported such as in tube-fed, very low birth weight infants and for hyperinsulinemic hypoglycemia [6)7)8)].

We first examined the safety and accuracy of the FGM in term neonates before using it in high-risk infants who need careful blood glucose management.

Differences between neonates and adults/older children

We used the Freestyle® Libre in mature infants; the local reactions were minor and reversible, and did not cause major adverse reactions or bacterial infections that left aftereffects. The puncture needle of the applicator during wear and purpura at the detached part of the sensor were found to be side effects that were not originally expected.

Compared to adults and older children who are stable and large in size, neonates have four distinct characteristics: skin fragility, immature blood coagulability, thin subcutaneous tissue and high water content of subcutaneous tissue.

(1) Skin fragility

Strong adhesion can be obtained by removing the vernix and amniotic fluid before application. There is a risk of skin irritation due to the adhesive tape when the sensor is attached and skin damage when the sensor is removed. It is necessary to use a detachment agent (remover), in consideration of the fragile epidermis.

(2) Immature blood coagulability

It is known that neonates soon after birth have low blood coagulability. In term neonates, clotting factor activity is 40-60% compared to the adult baseline [9]. When

wearing the Freestyle® Libre, only a soft sensor is left under the skin, but it is punctured with a slightly thick needle during wear. It is necessary to thoroughly check whether bleeding from the puncture site has stopped.

(3) Thinness of subcutaneous tissue

The Freestyle® Libre electrode has a length of 4 mm and is discreetly placed to measure glucose concentration in subcutaneous tissue. In a study that measured the subcutaneous fat thickness of the thigh by ultrasonography, it was reported to be 3.8 +/- 0.4 mm in term infants [10]. This means that in mature infants, the sensor electrodes are mostly contained within the subcutaneous fat, but in small and low birth weight infants, some of the electrodes may reach into the muscle and measure intramuscular glucose concentration. Glucose concentration decreases in the order plasma > subcutaneous fat > muscle. In addition, it is known that the fluctuation of intramuscular glucose concentration is delayed by about 30 min when the plasma glucose concentration fluctuates rapidly [11][12].

(4) Water content of subcutaneous tissue

A study examining the accuracy of diabetes patients reported that the accuracy of continuous blood glucose monitoring devices changed before and after dialysis [13]. Neonates have high water content in their subcutaneous tissue by nature as the water

lost as urine results in a physiological weight loss of around 5%. We believe that changes in subcutaneous tissue water content can affect the accuracy of continuous glucose monitoring devices.

Dissociation of CGM and blood glucose

We observed dissociation between the CGM and blood glucose values at 60 and 120 min after birth. We considered the following two points as the cause of the dissociation.

First, since the sensor has just been installed, the measured value of the sensor may not be stable and the value may have changed. From experience with diabetic children, the assumptions that the CGM data immediately after wear are unstable and dissociated from the blood glucose were made. In fact, a study examining accuracy in adults found that the accuracy on the first day of wearing the FGM was inferior to that from the second day onwards [14].

Second, glucose concentrations in the interstitial fluid may have differed from blood glucose levels, as blood glucose levels fluctuate widely in the early postnatal period. Continuous blood glucose monitoring devices have electrodes placed in subcutaneous tissue to measure the glucose concentration in the interstitial fluid

instead of the blood glucose level. When there is a rapid change in glucose concentration, it cannot follow, and dissociation occurs in the value. This is presumed to be since the movement of glucose concentration differs between blood and tissue. During a sharp drop in blood glucose level, the value obtained from the CGM falls after a delay, which may become an obstacle to the recognition of hypoglycemia [15].

Altogether, in the period immediately after birth, the Freestyle® Libre and direct blood glucose measurement should be used in combination, with careful observation of clinical findings.

Strengths

What is new in this research: i) the CGM device was applied to term neonates, not high-risk neonates, and its accuracy and safety were prospectively investigated. ii) the CGM scanning and blood sampling were performed hourly at 60, 120, 180, and 360 min after birth, which provided more pairwise data and allowed further hourly analysis.

In a similar study of at-risk neonates by Nishimura et al., the precision was analyzed separately for the period within 3 hours after birth and later, and they assumed that poor precision due to sensor instability led to large dissociations within

3 hours after birth [16]. In contrast, we performed hourly CGM scanning and blood sampling reading, finding that the CGM values tended to be low at 120 min and high at 60 min after birth compared to the blood sampling values. This suggests that the dissociation of CGM and blood sampling values observed in early post-natal period was caused by rapid changes in blood glucose which were not reflected in interstitial concentration, and not by sensor instability.

Limitations

We concluded that the dissociation of CGM data immediately after attachment was due to the inability of the FGM to follow rapid changes in blood glucose levels, but the influence of electrode instability immediately after attachment cannot be ruled out. Although it has been pointed out that there is a problem in discussing the dissociation between CGM and blood glucose levels using data gained immediately after attachment, which is said to have poor measurement accuracy, analyses such as the Bland-Altman analysis showed no particular tendency in the variation of measured values, and obtained results that could not be dismissed as by chance in analysis for each measurement time. From the above, we conclude that we have obtained enough data to stand up to discussion.

We may have underestimated dissociation because we substituted 39 mg/dL for values below the limit of measurement. However, based on the following two points, we believe that it is appropriate to perform statistical analysis by substituting 39 for LO: i) there is no discrepancy between the result derived by excluding LO and the result derived by substituting 39 for LO, ii) to assign 0 or 20 as the blood glucose level for neonates without any symptoms of hypoglycemia is inappropriate. The Freestyle® Libre only displays values as low as 40 mg/dL, so it may not be suitable for newborns whose blood glucose levels are lower than the levels in adults. However, if 'LO' is displayed, it can be determined that immediate therapeutic intervention is required.

Conclusions

The continuous glucose monitoring device was safe to wear on the neonate, and the CGM data correlated well with blood glucose levels. It should be borne in mind that when used in neonates immediately after birth or in infants with rapidly fluctuating blood sugar levels, there is dissociation between the CGM data and the blood glucose levels in the acute period when the blood glucose levels change rapidly.

Disclosure

The authors declare no conflict of interest.

Author contributions

O.A. drafted the initial manuscript. O.A. and S.I. conceived and designed the study. O.A. performed statistical analysis and interpreted the data. D.U., F.T., Y.S., Y.Y. and Y.F. revised the article critically for important intellectual content. All authors have contributed to the intellectual content of this manuscript and have approved the final manuscript as submitted.

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Figure legends

Figure 1 Details of measurement points

Figure 2 Bland-Altman analysis

LOA: limits of agreement, from -27.1 to 22.3

Figure 3 Clarke error grid [5)]

A black star indicates a clinically relevant point.

Gray circles indicate points displayed as 'LO'.

Substitution of 39 mg/dL for 'LO'.

Zone A are those values within 20% of the reference sensor.

Zone B contains points that are outside of 20% but would not lead to inappropriate treatment.

Zone D are those points indicating a potentially dangerous failure to detect hypoglycemia or hyperglycemia.

Figure 4 The CGM and blood glucose values by postnatal time

Gray boxes indicate data obtained from blood.

White boxes indicate data obtained from CGM.

Figures

Figure 1

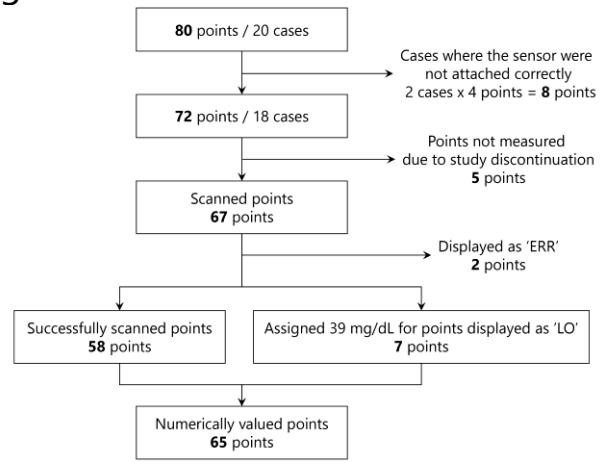

Figure 2

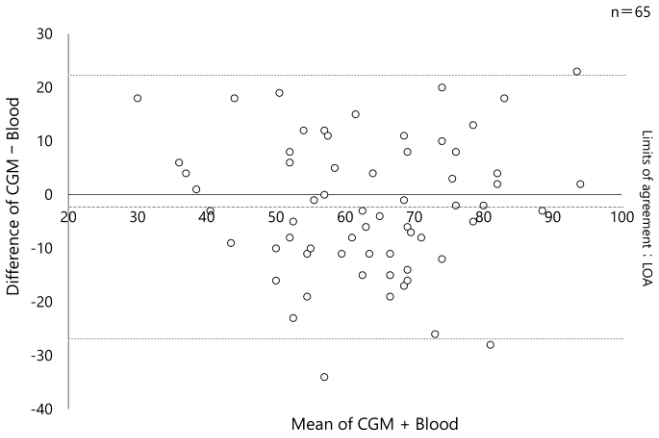

Figure 3

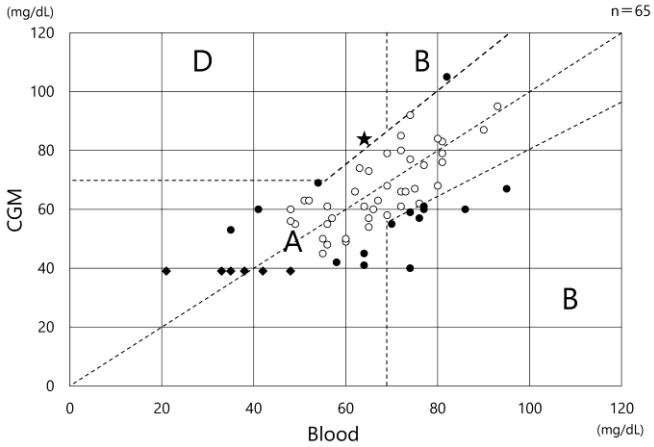

Figure 4

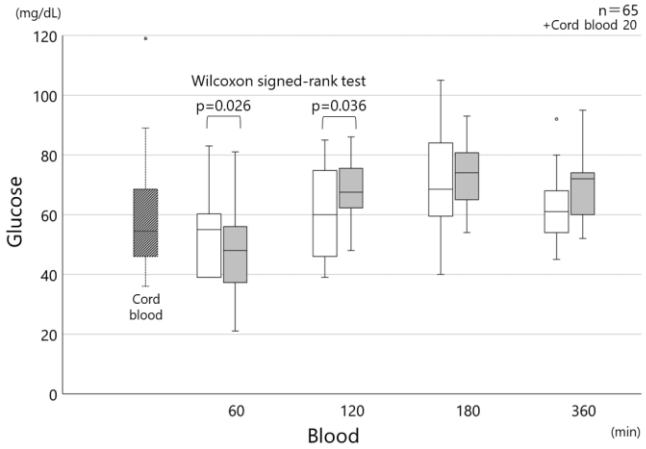

Table 1

Case characteristics

20 cases		Average	Range
Mother	Age (year)	33.7±5.1	21－41
	Para	2.4	1－4
	Gravaida	1.2	0－2
	Complication	APS(anti-phospholipid antibody syndrome)×1	
Delivery	Vaginal : Caesarean Section	7 : 13	
Infant	Male : Female	14 : 6	
	Gestational Age (weeks)	38.1±0.9	37-0/6－40-5/6
	Birth Weight (g)	2987.3±296.6	2494－3652
	Birth Length (cm)	49.1±1.9	44.4－52.5
	Birth Head Circumstance (cm)	34.1±0.8	32.5－35.3