Continuous Glucose Monitoring in Very Preterm Infants: A Randomized Controlled Trial

Alfonso Galderisi, MD,[a,b] Andrea Facchinetti, PhD,[c] Garry M. Steil, PhD,[d] Paulina Ortiz-Rubio, MD,[d] Francesco Cavallin, MS,[e] William V. Tamborlane, MD,[b] Eugenio Baraldi, MD,[a] Claudio Cobelli, PhD,[c] Daniele Trevisanuto, MD[a]

abstract

BACKGROUND AND OBJECTIVES: Impaired glucose control in very preterm infants is associated with increased morbidity, mortality, and poor neurologic outcome. Strategies based on insulin titration have been unsuccessful in achieving euglycemia in absence of an increase in hypoglycemia and mortality. We sought to assess whether glucose administration guided by continuous glucose monitoring (CGM) is more effective than standard of care blood glucose monitoring in maintaining euglycemia in very preterm infants.

METHODS: Fifty newborns ≤32 weeks' gestation or with birth weight ≤1500 g were randomly assigned (1:1) within 48-hours from birth to receive computer-guided glucose infusion rate (GIR) with or without CGM. In the unblinded CGM group, the GIR adjustments were driven by CGM and rate of glucose change, whereas in the blinded CGM group the GIR was adjusted by using standard of care glucometer on the basis of blood glucose determinations. Primary outcome was percentage of time spent in euglycemic range (72–144 mg/dL). Secondary outcomes were percentage of time spent in mild (47–71 mg/dL) and severe (<47 mg/dL) hypoglycemia; percentage of time in mild (145–180 mg/dL) and severe (>180 mg/dL) hyperglycemia; and glucose variability.

RESULTS: Neonates in the unblinded CGM group had a greater percentage of time spent in euglycemic range (median, 84% vs 68%, $P < .001$) and decreased time spent in mild ($P = .04$) and severe ($P = .007$) hypoglycemia and in severe hyperglycemia ($P = .04$) compared with the blinded CGM group. Use of CGM also decreased glycemic variability (SD: 21.6 ± 5.4 mg/dL vs 27 ± 7.2 mg/dL, $P = .01$; coefficient of variation: 22.8% ± 4.2% vs 27.9% ± 5.0%; $P < .001$).

CONCLUSIONS: CGM-guided glucose titration can successfully increase the time spent in euglycemic range, reduce hypoglycemia, and minimize glycemic variability in preterm infants during the first week of life.

Departments of [a]NICU, Women's and Child's Health and [c]Information Engineering, University of Padova, Padova, Italy; [b]Endocrinology Section, Department of Pediatrics, Yale University, New Haven, Connecticut; [d]Boston Children's Hospital, Boston, Massachusetts; and [e]Independent Statistician, Padova, Italy

Dr Galderisi conceived and designed the trial, enrolled patients, and drafted the manuscript; Mr Facchinetti contributed to the trial design, analyzed the data, and drafted the manuscript; Prof Steil contributed to the study design, conceived and developed the control algorithm, analyzed the data, and critically revised the manuscript; Dr Ortiz-Rubio contributed to the design of the study and to the development of the control algorithm and revised the manuscript; Mr Cavallin analyzed the data and contributed to the interpretation of the results and drafting of the manuscript; Prof Tamborlane analyzed and interpreted the data and critically revised the manuscript; Prof Baraldi enrolled patients, interpreted the data, and critically revised the manuscript; Prof Cobelli and

WHAT'S KNOWN ON THIS SUBJECT: Both hypoglycemia and hyperglycemia, during the first week of life, are associated with poor neurologic outcomes and increased mortality in preterm infants. To date, there are no effective strategies for effectively and continuously adapting glucose infusion that ensures tight glucose control.

WHAT THIS STUDY ADDS: In this randomized controlled trial, we adopted continuous subcutaneous glucose monitoring coupled with computer-based algorithm for titration of glucose infusion during the first week of life in preterm infants. This approach resulted in an increase of time spent in tight glycemic range.

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Maintenance of euglycemia is critical in neonatal care of preterm newborns as impaired glucose control is associated with higher mortality.[1,2] Hyperglycemia occurs in >60% of preterm infants during the first week of life[3] and has been associated with adverse short-term outcomes[3,4] and a worsening of neurosensory development at 2 years of life.[5] Prolonged hypoglycemia has also been demonstrated to negatively impact neurodevelopmental outcomes.[5–7]

In previous studies, the safety and efficacy of insulin infusion to reduce hyperglycemia have been evaluated,[1,4] but this approach has led to an increase of hypoglycemic events with either no improvement in predefined outcomes[1,3] or increased mortality before 28 days of life in large randomized trials.[1]

However, new technologies such as continuous glucose monitoring (CGM) systems and advanced control algorithms for real-time glucose or insulin titration[3] can better incorporate a dynamic measure of glucose change over time and potentially allow attainment of tight glycemic control in a safe manner. Although CGM accuracy and safety in preterm infants has been validated in several studies[4,5] and CGM-guided glucose control algorithms have been used in children and adults,[3] this approach has never been studied in neonates. Moreover, no definitive data have emerged revealing that CGM with or without a control algorithm can successfully improve glucose control in preterm newborns.

Our objective in the current study was to determine if the use of a CGM-enhanced advanced control algorithm could increase the time spent in euglycemic range, thus reducing both hypoglycemia and hyperglycemia in very preterm infants.

METHODS

Study Design

We performed a prospective randomized controlled trial at the NICU of the University Hospital of Padua (Italy). Eligible infants were randomly assigned to 1 of 2 study arms within 48 hours of birth: a treatment group in which glycemic control was achieved by using an unblinded CGM with active alarms coupled with a proportional-integrative-derivative (PID) control algorithm (unblinded-CGM [UB-CGM]), or a control group in which a blinded CGM was used and glucose infusion rate (GIR) was calculated on the basis of standard-of-care blood glucose levels measured by glucometer (blinded-CGM [B-CGM]). Patients were randomly assigned by using electronically generated block randomization of 5 blocks of 10 subjects per block (www.sealedenvelope.com) with an allocation ratio 1:1 to the randomization groups. Opaque envelopes containing the allocation group were sealed and sequentially numbered according to an electronically generated randomization list. An officer not involved in the study performed the procedure.

Data were electronically anonymized by using an individual alphanumeric code and analyzed by investigators not involved in patient enrollment or data collection. The trial was approved by the Institutional Ethics Committee of the University Hospital of Padua (3440/AO/15) and designed as a nonprofit research project by the principal investigators and collaborators of the NICU of University of Padua (Italy), the Department of Bioengineering (University of Padua, Italy), and Boston Children's Hospital (Harvard Medical School, Boston, MA). Clinicaltrials.gov identifier NCT02583776.

Participants

All infants born ≤32 weeks' gestation or birth weight ≤1500 g at University Hospital of Padua, being <48 hours after birth, were eligible for the study. Newborns with congenital malformations, chromosomal abnormalities, or a birth weight of <500 g were excluded. Written informed consent was obtained from a parent or guardian of each infant at study entry.

Procedures

All newborns included in the study wore a G4 Platinum CGM system (Dexcom, Inc, San Diego, CA). CGM sensors were placed on the lateral side of the thigh after adequate disinfection of the site. Two minutes before the procedure, 0.3 mL of sucrose 12% was administered to the patient to minimize pain associated with sensor insertion. The device was worn for a maximum of 7 days with calibrations performed at least twice per day, as per manufacturer's instructions. Calibrations were performed by using capillary blood glucose values measured by using an Accu-Chek Inform II glucometer (Roche Diabetes Care, Indianapolis, IN). In case of detachment or malfunction, the device was replaced no more than once. The system was removed if the patient needed to be transferred to another unit or hospital. All enrolled patients had a venous line to ensure glucose intakes as per protocol.

UB-CGM Group

Newborns assigned to the UB-CGM group wore the CGM device with active alarms for hypoglycemia (<72 mg/dL) and hyperglycemia (>144 mg/dL). Threshold CGM values of <47 and >180 mg/dL triggered alarms that mandated an immediate adjustment of the GIR and, in cases in which hypoglycemia (<47 mg/dL) was anticipated to occur within 15 minutes, an immediate glucose bolus. Changes in the GIR were calculated

by using the PID control algorithm with CGM sensor glucose and its rate of change used to anticipate hypoglycemia. CGM glucose and CGM glucose rate of change (−3 to +3 mg/dL per minute in increments of 1 mg/dL per minute) were entered into a dedicated laptop computer every 3 hours. Target glucose was set at 108 mg/dL (range 72–144 mg/dL).

The starting GIR for patients with an initial glucose value in the predefined target range (72–144 mg/dL) was 7.5 g/kg per day. For patients with an initial glucose value above or below the target range, the initial GIR rate was adjusted based on the difference between the initial glucose value and targeted glucose value (midpoint of target range), and estimated glucose rate of change (−3 to +3 mg/dL per minute in increments of 1 mg/dL per minute as reported by the CGM). Subsequent changes in the GIR were affected every 3 hours following the same PID rules (Supplemental Information). Minimum daily intake of carbohydrates, defined by the European Society for Pediatric Gastroenterology, Hepatology, and Nutrition (ESPGHAN) for preterm infants,[6] was preprogrammed into the PID algorithm with the integral (I-term) increased as needed.

B-CGM Group

Newborns assigned to the B-CGM group wore the CGM device with blinded monitor and no alarms (data used for retrospective calculation of performance metrics). GIR was adjusted based on point-of-care blood glucose measurements performed, at minimum, every 8 hours as is standard care at the University Hospital of Padua. We adopted the same starting rule for GIR as UB-CGM group but without accounting for the derivative component (D-term of the PID algorithm) because of the lack of rate of change information in this group. Glucose measurements were entered into an Excel spreadsheet running the same PID algorithm, without the D-term of the PID algorithm and without calculation of the anticipated glucose value 15 minutes into the future (anticipated value requires the glucose rate of change at the time of measurement to be known). The algorithm was again modified to ensure compliance with ESPGHAN recommendations for preterm infant nutrition.[6] Additional glucose tests were performed in case of detection of hypoglycemia or hyperglycemia 30 minutes after glucose adjustment and in the presence of clinically relevant events (acidosis, electrolytic imbalance, vital parameters changes, and procedures).

PID Control Algorithm

All PID control algorithms effect changes in a control output (here, GIR) in proportion (P) to the difference between the controlled variable (here CGM glucose) and a target, the integral (I) of the difference between the controlled variable and target, and the rate of change of the controlled variable (derivative; D). For the current study, the algorithm was modified to increase integral term each morning in accordance with the ESPGHAN recommendations for preterm infant nutrition[6] and further modified to allow study staff to override the recommended GIR (number of overrides recorded). Further details of the algorithm are provided in Supplemental Information Protocol Section A6.

Outcomes

Primary outcome was the percentage of time spent in euglycemic range (72–144 mg/dL) during the first 7 days of life.[1,5] Secondary outcomes included the time spent in mild and severe hypoglycemic and hyperglycemic ranges defined as: mild hypoglycemia (M-HYPO) (47–71 mg/dL); severe hypoglycemia (S-HYPO) (<47 mg/dL); mild hyperglycemia (M-HYPER) (145–180 mg/dL); and severe hyperglycemia (S-HYPER) (>180 mg/dL).[1,5] Glycemic variability (GV) was assessed by the mean glucose concentration, its SD and coefficient of variation calculated as the percent value of SD divided by the mean glucose.[8]

Clinical outcomes evaluated included: requirement for intubation in delivery room, surfactant within the first 24 hours of life, grade III/IV intraventricular hemorrhage, late onset sepsis (at least 1 positive blood culture result after 72 hours of life) recorded within 28 days of life, oxygen requirement at 36 weeks of age, mortality at 28 days and before discharge,[7] occurrence of skin lesions,[9] and changes in weight. Newborn small for gestational age was defined in presence of a birth weight <10th percentile for gestational age. Preterm-premature rupture of membrane indicated rupture of membranes before the onset of labor in presence of a gestational age <37 weeks' gestation.

Statistical Analysis

Power was estimated by using time in target reported for infants aged 0 to 36 months admitted to a cardiac ICU and controlled with a CGM-enabled algorithm similar to that used in the current study. On the basis of these data, we estimated 42 subjects (21 subjects in each arm[3]) would be needed to obtain 80% power to detect an improvement in time in target. Enrollment for the current study was set at 50 subjects to allow at most 15% of the infants being lost to analysis.

Analysis was performed on all the patients wearing the CGM for at least 48 hours. Continuous data are expressed as median and interquartile range (IQR) or mean ± SD, as appropriate. Percentage of time in target and in hypoglycemic and hyperglycemic ranges are expressed as median (IQR) with the effect of the intervention (UB-CGM versus B-CGM) estimated by using a Poisson regression model, adjusting for

clinically relevant confounders (ie, sex, gestational age, and birth weight). The logarithm of the available number of readings was included in the model as offset.

The number of events of S-HYPO and S-HYPER for each patient was compared between groups by using a Poisson model. An event was defined as lasting for >15 consecutive minutes.

Binary variables were analyzed with Fisher's exact test, continuous variables were analyzed with the use of Wilcoxon rank-sum tests. Two-way repeated measures analysis of variance was adopted for weight analysis. Continuous GIR graphs are reported as mean with 95% confidence interval (CI) by using all available data. A P <.05 was considered statistically significant. Statistical analysis was performed by using R 3.2.2 software (R Foundation for Statistical Computing, Vienna, Austria) or GraphPad Prism version 7.01 (GraphPad Software, La Jolla, CA), power calculation for the primary outcome (time in target) was performed by using NQuery (Statistical Solutions, Boston, MA).

RESULTS

Patient Characteristics

A total of 251 neonates were admitted to the NICU during the study period and were evaluated for study eligibility. Of these, 195 did not meet inclusion criteria, 2 died in the delivery room, and 4 were transferred to another hospital. The remaining 50 neonates (27 girls) were enrolled from November 1, 2015, to March 30, 2016. Forty-four neonates completed the entire 7-day protocol (median study interval 6.7 days [5.9–6.9]); 4 in the UB-CGM group were transferred at the request of the parents to a hospital closer to their home, 2 (1 infant from the UB-CGM and 1 from B-CGM) required sensor replacement more than once with monitoring

TABLE 1 Baseline Characteristics of the Intention-to-Treat Population

	UB-CGM, *N* = *25*	B-CGM, *N* = 25
Neonates		
Gestational age (wk)	30 (29–31)	30 (28–31)
Birth wt (g)	1170 (1100–1595)	1300 (1100–1760)
Small for gestational age, *n* (%)	4 (16)	0
Twins, *n* (%)	6 (24)	11 (44)
Sex (male:female)	10:15	13:12
CRIB score	5 (2–8)	5 (2–8)
Mothers		
Maternal diabetes, *n* (%)	4 (16)	1 (4)
PPROM, *n* (%)	3 (12)	2 (8)

Clinical risk index for babies[10]; data expressed as *n* (%) or median (IQR). CRIB, clinical risk index for babies; PPROM, preterm-premature rupture of membrane.

discontinued per protocol (Fig 1). Forty-eight neonates were of non-Hispanic white ethnicity, and 2 were non-Hispanic African American, with the non-Hispanic African American randomly assigned 1:1 to UB-CGM and B-CGM groups.

Neonatal and maternal characteristics were similar in the 2 groups at admission (Table 1). Median study interval was not different between the 2 groups: 6.62 days (6.50–6.75]) versus 6.65 days (5.74–6.90) for UB-CGM and B-CGM, respectively (P = .62). Infants in the UB-CGM group had 7.6% (IQR 1.9%–10.3%) compared with 9.9% (IQR 5.0%–12.9%) weight loss during the study period.

The median number of blood glucose test per day was lower in UB-CGM

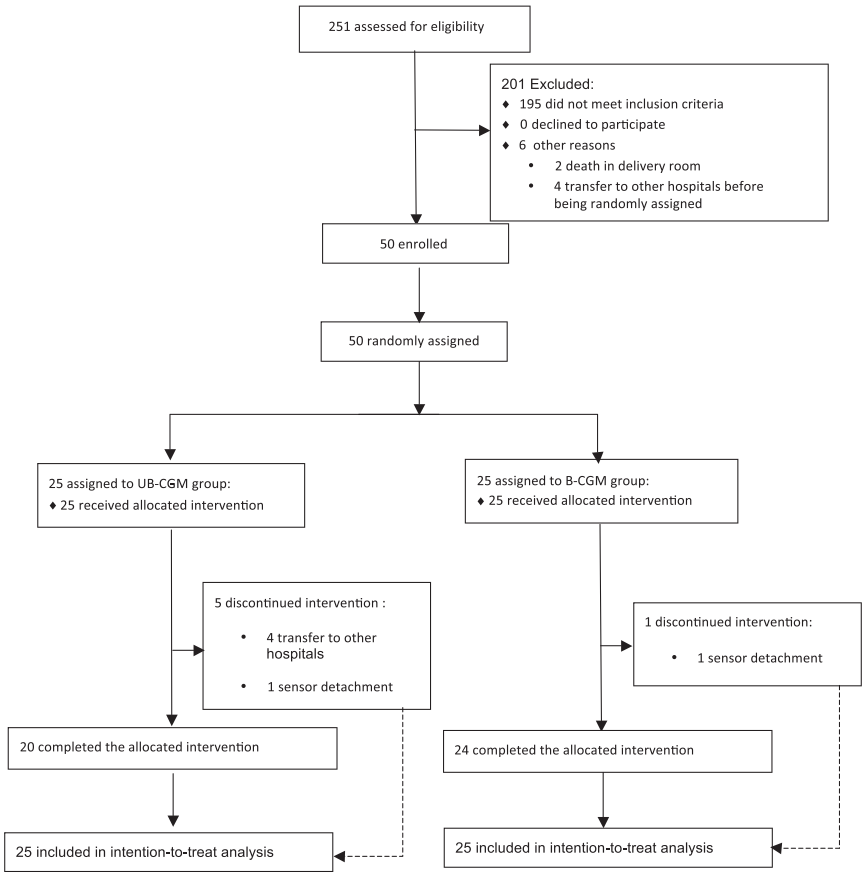

FIGURE 1
Trial profile.

group than B-CGM group (2.40 tests per day [2.217–2.63] versus 2.59 tests per day [2.35–2.92] in the UB-CGM and B-CGM groups, respectively; $P = .03$).

Glucose Concentration and GIR by Day

Overall mean glucose concentrations were similar during the 7-day protocol in UB-CGM and B-CGM groups (97.2 mg/dL [IQR 93.6–100.8] vs 102.6 mg/dL [IQR 100.8–106.2], respectively (Fig 2A). GIR was increased over time in both groups per protocol with the rate tending to be higher in the UB-CGM versus B-CGM (13.9 g/kg per day [IQR 10.7–17.2] vs 11.0 g/kg per day [IQR 9.1–13.0]) (Fig 2B, Table 2). During the course of the study the PID algorithm made 1642 recommendations, of which 1541 were accepted (93.8%).

The 2 groups were comparable for the intakes of other nutrients over the study period, including proteins (3.04 g/kg per day [2.93–3.11] in neonates from UB-CGM versus 3.04 g/kg per day [2.99–3.10] in B-CGM [$P = .915$]) and lipids (0.49 g/kg per day [0.45–0.51] in UB-CGM vs 0.49 g/kg per day [0.44–0.52] in the B-CGM group [$P = .930$]).

Primary Outcome: Time in Target

Unadjusted median time in glycemic target range was 84% (IQR 77%–89%) in UB-CGM group vs 68% (IQR 65%–77%) in B-CGM group ($P < .001$) (Fig 3), with similar results after multivariable analysis adjusting for sex, gestational age, and birth weight (mean time in target of 83% [95% CI, 79%–87%] in UB-CGM and of 71% [95% CI, 67%–76%] in B-CGM [$P < .001$]). Individual profiles are reported in Supplemental Information for both UB-CGM and B-CGM groups.

Secondary Outcomes: Time in Hypoglycemia, Hyperglycemia, Glucose Variability

UB-CGM subjects spent less time than B-CGM subjects in S-HYPO (0.2% [IQR 0–0.7] vs 1.5% [IQR 0.2–4.7], $P = .002$) and in M-HYPO (12.1 [IQR 5.1–16.3] vs 16.9% [IQR 9.8–26.0], $P = .03$). Multivariable analysis revealed an adjusted mean time in S-HYPO of 0.6% (95% CI, 0.3–1.4) in UB-CGM and of 2.2% (95% CI, 1.4–3.3) in B-CGM ($P = .007$). Multivariable analysis revealed an adjusted mean time in M-HYPO of

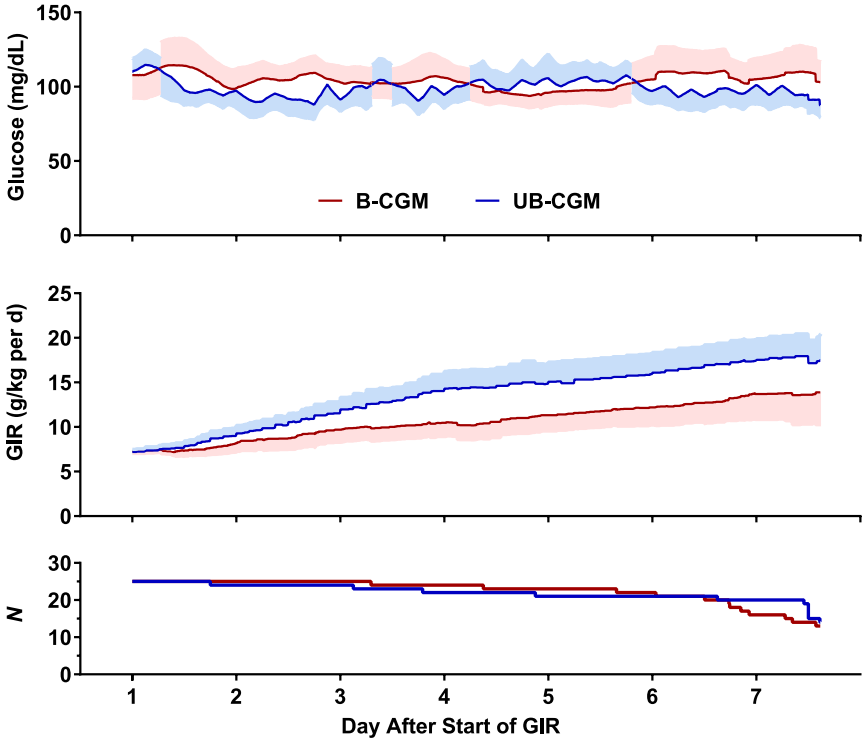

FIGURE 2
Mean glucose, mean GIR, and completion of study interval. A, CGM profiles (mean ± 95% CI) for newborns managed with a computer-guided GIR algorithm on the basis of CGM readings (UB-CGM) or point-of-care blood glucose readings (B-CGM). B, GIR delivered during the study. C, Total number of subjects in the study. Data are shown for all CGM values used to affect GIR. Day 1 indicates the first day CGM values were used to affect GIR.

TABLE 2 Clinical Outcomes

	B-CGM, $N = 25$	UB-CGM, $N = 25$	P
IVH third or fourth	2 (4)	0	.49
Sepsis (late)[a]	2 (4)	0	.49
Pneumothorax	3 (6)	0	.24
Intubation in delivery room	9 (18)	6 (12)	.58
Surfactant <24 h	12 (24)	9 (18)	.62
O_2 requirement at 36 wk	1 (2)	0	.99
Percentage of weight loss during the study	7.6 (1.9–10.3)	9.9 (5.0–12.9)	.22
GIRs (g/kg per d)	11.0 (9.1–13.0)	13.9 (10.7–17·2)	.02
Mortality at 28 d	0	0	—
Mortality before discharge	1 (2)	0	.99
Days before discharge[b]	46 (40–74)	51 (37–63)	.59

Data expressed as *n* (%). IVH, intraventricular hemorrhage; —, not applicable.
[a] Recorded up to 28 d of life.
[b] Median (IQR).

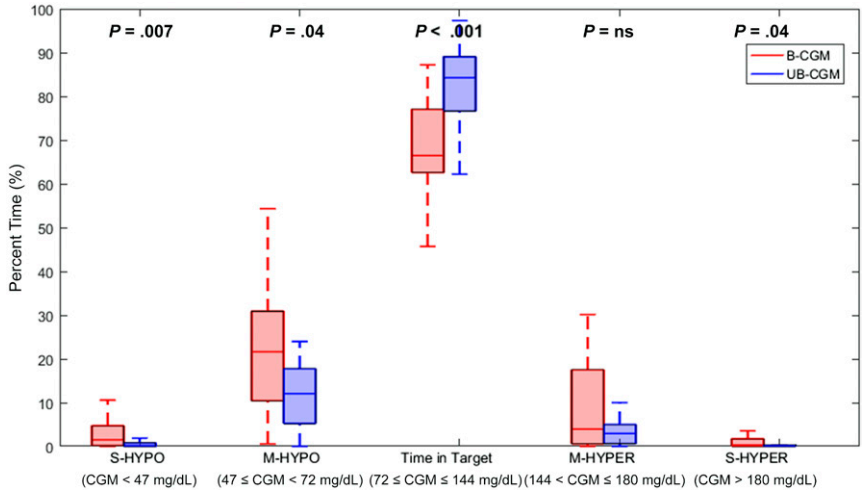

FIGURE 3

Primary and secondary outcomes. Percentage of time in target time spent in mild and S-HYPO and S-HYPER in B-CGM and UB-CGM groups is shown. Data are expressed as intention-to-treat analysis (median, IQR). ns, not significant.

12% (95% CI, 9–17) in UB-CGM and of 18% (95% CI, 14–22) in B-CGM ($P = .04$). Subjects in UB-CGM and B-CGM groups spent similar time in M-HYPER (2.7% [IQR 0.8–4.1] vs 3.6% [IQR 0.6–12.5], respectively; $P = .13$). Multivariable analysis revealed an adjusted mean time in M-HYPER of 4% (95% CI, 2–7) in UB-CGM and of 7% (95% CI, 5–10) in B-CGM ($P = .12$). Median time in S-HYPER was 0.0% (IQR 0.0–0.3) in UB-CGM and 0.3% (IQR 0.0–1.6) in B-CGM ($P = .14$). Multivariable analysis revealed an adjusted mean time in S-HYPO of 0.4% (95% CI, 0.2%–1.0%) in UB-CGM and of 1.2% (95% CI, 0.7–2.0) in B-CGM ($P = .04$) with the UB-CGM group having a significant reduction in the number of severe hypoglycemic events (1.4 ± 2 vs 4.7 ± 6.2 events per subject, $P = .01$) and number of severe hyperglycemic events per subject (0.8 ± 1.6 vs 2.2 ± 3.3 events per subject, $P = .04$).

Intersubject GV, as measured by SD, was lower in the UB-CGM group (21.6 ± 5.4 mg/dL vs 27 ± 7.2 mg/dL, $P = .01$). Mean glucose values were not different (97.2 ± 10.8 mg/dL vs 97.2 ± 7.2 mg/dL, respectively; $P =$ not significant) thereby leading to a lower coefficient of variation in the UB-CGM groups (22.8% ± 4.3% vs 27.9% ± 5.0%; $P < .001$). As shown in Fig 4, by the mean of cumulative distribution of glucose values within the 2 groups, the reduction of the variability (represented by the shaded area around the median of each group) evidences how the use of the CGM-guided GIR algorithm allows tighter control of glucose concentration in the target, reducing the risk of edge-case patients, with the percentage of values below the 47 and 72 mg/dL significantly lower in UB-CGM and the time in range (72–144 mg/dL) significantly increased (Fig 4).

Clinical Outcomes and Adverse Events

Infants were monitored for signs of adverse events at sensor insertion sites, such as infection, irritation, subcutaneous hemorrhage, and subcutaneous sensor wire breakage, with the events reported (Fig 5). Detachment of the device more than once occurred in 2 subjects that discontinued the intervention as per protocol (Fig 1). The 2 groups were comparable with respect to the short-term clinical outcomes as reported in Table 2. Use of CGM did not affect weight at the end of the study (1335 ± 75.8 g vs 1323 ± 67.9 g; $P = .91$), which remained stable over the 7-day period ($P = .32$) with no interaction between study day and treatment arm ($P = .52$).

DISCUSSION

In the current study, we demonstrate that CGM-guided glucose infusion titration improves glycemic control in very preterm infants by increasing time in euglycemia, reducing both hypoglycemia and S-HYPER (along with GV) compared with glycemic control achieved with standard of care intermittent blood glucose sampling. Previous studies on preterm infants have largely been focused on insulin administration for hyperglycemia management[11] and have not explicitly linked a CGM with a control algorithm to guide adjustments in the insulin infusion rate.[12,13] In contrast, we highlight that linking a CGM to control algorithm guiding glucose titration alone can successfully achieve glucose control in this population without need for insulin. Moreover, it can do so without sacrificing adequate nutrition to sustain growth in very preterm infants, as evidenced by loss of <10% of birth weight in neonates belonging to the UB-CGM treatment group and following the minimum increase in glucose administration of 1 g/kg per day GIR recommended by the ESPGHAN.[6] That we achieved these results indicates that preterm infants are capable of increasing glucose disposal without need of additional insulin. This finding is consistent with the one obtained in the Neonatal Insulin Replacement Therapy in Europe trial, in which the investigators did not find an association between the rate of glucose infusion and risk of hyperglycemia.[2,14] Our results suggest that hyperglycemia, in this population, is not necessarily due to impaired insulin secretion but rather to inappropriate glucose titration. The ability to rapidly change GIRs allows

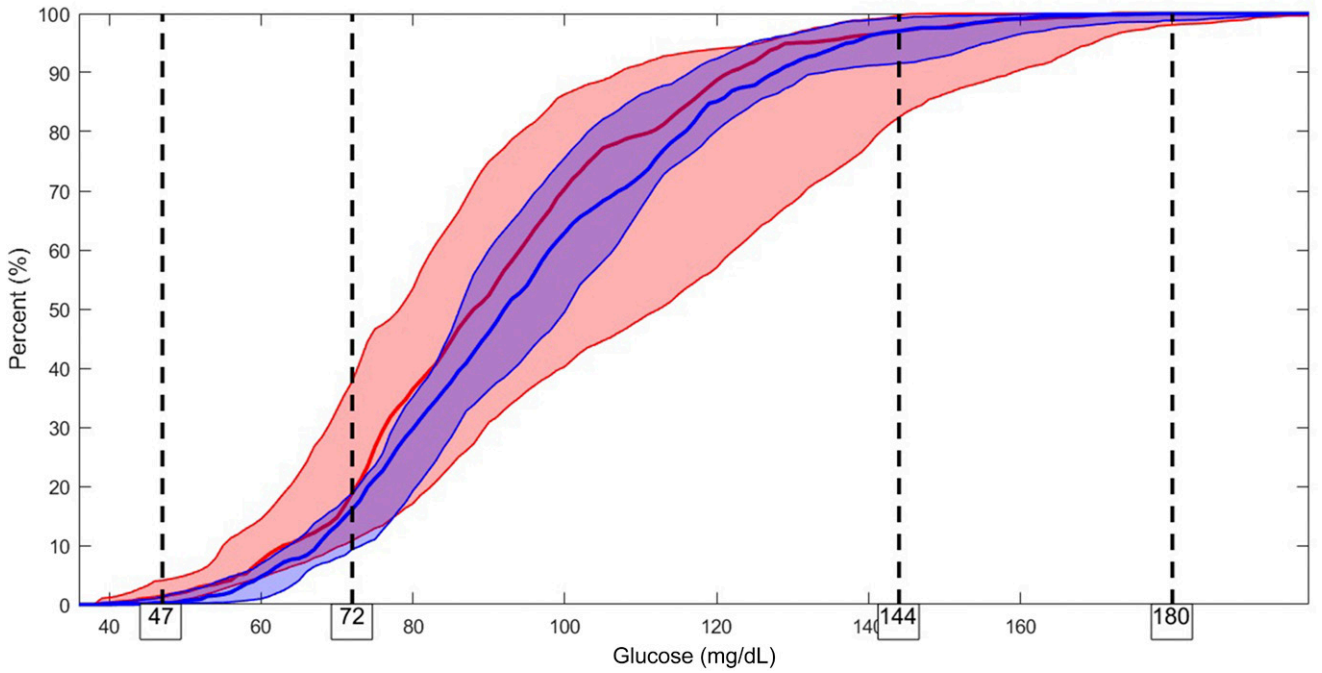

FIGURE 4
Glucose variability. The x-axis reports the glucose concentration, and the y-axis reports the mean (±SD) cumulative distribution function of the 2 groups; vertical lines indicate mild hypoglycemia, mild hyperglycemia, S-HYPO, and S-HYPER.

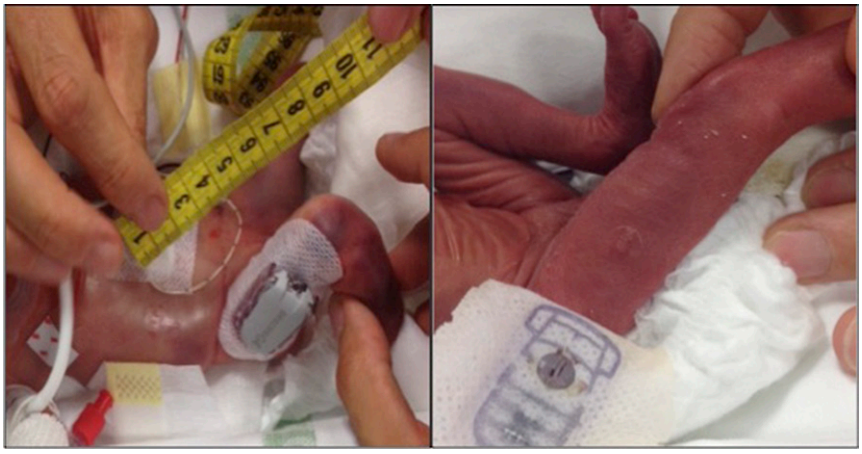

FIGURE 5
Safety monitoring. The left panel shows CGM in situ, and the right panel shows skin after removal of the device.

prevention of both hypoglycemia and hyperglycemia while maintaining glucose intake and weight gain goals.[6]

The strengths of our study are a high study completion rate for enrolled subjects and adherence to the study arm protocol to which subjects were randomly assigned. Combined use of CGM and a control algorithm allowed us to maximize both safety and reproducibility. Fine tuning changes to achieve the target glucose value on the basis of the rate of variation of CGM values (derivative component of algorithm) along with intervening in the mild hypoglycemic and hyperglycemic ranges, allowed prevention of both S-HYPO and S-HYPER, reducing significantly both the time out of range and the severe hypoglycemic events requiring an immediate correction (from 4.7 ± 6.2 to 1.4 ± 2 events per patient). Additionally, we were able to reduce glucose variability in UB-CGM group because of the fine-tuning adaption of glucose adjustment performed by the mean of a control algorithm, effecting a glucose measure that is known to increase mortality in very low birth weight infants.[15]

A major limitation of this study was the lack of power to detect any effect on clinical outcomes derived from the tested intervention. The control group demonstrated a higher number of adverse clinical outcomes, not statistically significant, including late onset sepsis and third to fourth degree intraventricular hemorrhage (Table 2), that suggests the need for a larger trial which is aimed at testing the long and short clinical effects of the studied approach. We cannot exclude that the reduced use of central line for blood glucose test in UB-CGM group could have positively influenced the risk for late onset sepsis as previously described.[9]

The current study included only a limited number of extremely low birth weight infants whose glucose homeostasis is known to be different from neonates with higher birth weight, mainly due to the higher insulin resistance suggesting that specific interventions should be tailored and investigated for this gestational age.[16–19]

We adopted point-of-care glucose meter testing, as previously described,[3,9] because it provided real-time plasma glucose values for immediate calibration of CGM (as per manufacturer instruction) and for adjustments of GIRs, although the gold standard for glucose monitoring in at-risk newborns remains laboratory measurements of plasma glucose.

An additional limit of our study includes the lack of investigator blinding. However, this was partially mitigated by the introduction of an electronic spreadsheet for glucose adjustments in the blinded group. The spreadsheet ran a modified algorithm designed to propose the ideal daily glucose intake for preterm nutrition[6] and to perform fixed corrections to target the glycemic range according to current recommendations, with the derivative component equal to 0 due to the lack of glucose rate of change measured in the UB-group by CGM. All the adjustments were made according to blood glucose sampling, performed at least 3 times per day. This approach standardized the behavior of investigators in both the study arms and enhanced reproducibility. However, although the use of spreadsheet in the control arm reduced the potential for bias and increased reproducibility, it is not a standard of care in the ICU and prevents us from drawing any conclusions regarding the use of CGM with PID control versus standard of care per se.

Our experience during this trial was that CGM devices are well received by parents given that all families approached accepted participation in the study. Additionally, we found CGMs to be safe and encountered no CGM-related adverse events. Nevertheless, routine use of CGM-driven control algorithms in the NICU could be burdensome for the personnel because they require logging of CGM values in an Excel spreadsheet every 3 hours and CGM calibration at least twice a day. Such limitations will likely be of short duration, however, as CGM technology continues to rapidly improve. CGMs now have Bluetooth capability that will allow remote transmission of CGM data to a centralized platform with an automated advisor, modeled as described for the artificial pancreas pediatric studies.[8] New generation CGM models are also now expected to require only a single daily calibration and to last 10 instead of 7 days, thus potentially reducing the burden of frequent blood glucose sampling in these patients.

Future studies of larger samples size are needed to assess long-term clinical outcomes related to this form of glucose management in very preterm infants.[20–23]

CONCLUSIONS

We provide the first evidence that CGM, combined with an algorithm for adjusting glucose infusion, can effectively and safely increase the percentage of time spent in euglycemia with a reduced risk of both hypoglycemia and hyperglycemia and a decrease of glucose variability in very preterm infants.

ACKNOWLEDGMENTS

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CGM materials for the study were provided by Dexcom Inc, San Diego, California. Dexcom Inc had no role in study design, data collection, data analysis, data interpretation, or writing of the writing of the report.

ABBREVIATIONS

B-CGM: blinded continuous glucose monitoring
CGM: continuous glucose monitoring
CI: confidence interval
ESPGHAN: European Society for Pediatric Gastroenterology, Hepatology, and Nutrition
GIR: glucose infusion rate
GV: glycemic variability
IQR: interquartile range
M-HYPER: mild hyperglycemia
M-HYPO: mild hypoglycemia
PID: proportional-integrative-derivative
S-HYPER: severe hyperglycemia
S-HYPO: severe hypoglycemia
UB-CGM: unblinded continuous glucose monitoring

Dr Trevisanuto designed the trial, analyzed the data, and critically revised the manuscript; and all authors approved the final manuscript as submitted and are responsible for the accuracy and the integrity of the data.

This trial has been registered at www.clinicaltrials.gov (identifier NCT02583776).

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Address correspondence to Alfonso Galderisi, MD, Pediatrics Endocrinology, Yale University, 333 Cedar St, New Haven, CT 06510. E-mail: alfonso.galderisi@yale.edu

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