Strict glycaemic control in very low birthweight infants using a continuous glucose monitoring system: a randomised controlled trial

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ABSTRACT

Objective To evaluate the efficacy of a strict glycaemic control protocol using a continuous glucose monitoring (CGM) in infants at high risk of dysglycaemia with the aim of reducing the number of dysglycaemic episodes.

Design Randomised controlled trial.

Setting Neonatal intensive care unit, Fondazione Policlinico Universitario Agostino Gemelli, IRCCS, Rome.

Patients All infants <1500 g fed on parental nutrition (PN) since birth were eligible. A total of 63 infants were eligible and 48 were randomised.

Intervention All participants wore a CGM sensor and were randomised in two arms with alarms set at different cut-off values (2.61–10 mmol/L (47–180 mg/dL) vs 3.44–7.78 mmol/L (62–140 mg/dL)), representing the operative threshold requiring modulation of glucose infusion rate according to an innovative protocol.

Main outcome measures The primary outcome was the number of severe dysglycaemic episodes (<2.61 mmol/L (47 mg/dL) or >10 mmol/L (180 mg/dL)) in the intervention group versus the control group, during the monitoring time.

Results We enrolled 47 infants, with similar characteristics between the two arms. The number of dysglycaemic episodes and of infants with at least one episode of dysglycaemia was significantly lower in the intervention group (strict group): respectively, 1 (IQR 0–2) vs 3 (IQR 1–7); (p=0.005) and 12 (52%) vs 20 (83%); p=0.047. Infants managed using the strict protocol had a higher probability of having normal glycaemic values: relative risk 2.87 (95% CI 1.1 to 7.3). They spent more time in euglycaemia: 100% (IQR 97–100) vs 98% (IQR 94–99), p=0.036. The number needed to treat to avoid dysglycaemia episodes is 3.2 (95% CI 1.8 to 16.6).

Conclusion We provide evidence that CGM, combined with a protocol for adjusting glucose infusion, can effectively reduce the episodes of dysglycaemia and increase the percentage of time spent in euglycaemia in very low birthweight infants receiving PN in the first week of life.

What is already known on this topic?

- Being real-time glucose monitoring systems new tools for neonatal care, research is focusing on new operative thresholds for neonatal hyperglycaemia and hypoglycaemia.
- Continuous glucose monitoring system (CGMS)-guided glucose titration is superior to standard administration of glucose infusion.

What this study adds?

- We studied a simple protocol for glucose infusion, based on CGMS and glycaemic percentiles.
- This can reduce dysglycaemia episodes in very low birthweight neonates fed by parenteral nutrition in the first week of life.

INTRODUCTION

Very low birthweight (VLBW) infants are exposed to fluctuations in blood glucose levels. Both hyperglycaemia and hypoglycaemia have been related with increased mortality and morbidity.[1 2] There is still a need for studies to improve glucose control in VLBW infants.[3]

The gold standard for glucose assessment in neonatal intensive care units (NICU) is plasma glucose measured with enzymatic methods,[4] through finger-stick capillary blood and point-of-care (POC) blood glucometer (GTX).[5] This method, however, produces only punctual values and does not allow a real-time (RT) monitoring of glycaemia. Moreover, there is controversy over the values of normoglycaemia in neonatal population[6 7] and no consensus on the pragmatic definition of the threshold of plasma glucose concentration and the time needed to cause neurological damage.[8 9]

New technologies such as the continuous glucose monitoring system (CGMS) can be used to investigate glucose homeostasis and some studies showed its use is safe and reliable.[9–11] We have conducted a prospective study using Medtronic's CGM, validating safety and feasibility of this CGMS, in VLBW infants fed with parenteral nutrition (PN) during their first week of life and describing the distribution of glycaemic values in this population.[12] In this study, 10° and 90° glycaemic percentiles were similar to the limits of glycaemia chosen as optimal range in other studies both in children and neonates.[13 14] New glucose infusion protocols,[10 13 15] based on RT monitoring, have been proposed.

Blinded CGMS has been investigated in preterm infants within clinical trials[11 16 17] and studies

of RT devices have shown a benefit in the prevention of hypoglycaemia.[18]

These data highlighted the possibility of using RT monitoring to improve the management of dysglycaemia.

Our aim was to investigate, using a CGMS on infants at high risk of dysglycaemia, whether a strict glycaemic control could reduce dysglycaemic episodes.

METHODS

We designed a randomised controlled trial with two arms of intervention.

All VLBW infants born at Fondazione Policlinico Universitario Agostino Gemelli IRCCS Catholic University Hospital fed with PN by the first day of life were eligible for the study. Written informed consent was obtained from the parents before enrolment.

Newborns with congenital anomalies or chromosomic disorders, those weighing less than 500 g, infants not wearing a CGM for more than 96 hours and infants who needed more than one sensor replacement were excluded. Once the parents gave informed consent, every eligible infant had a CGM sensor placed and was randomly assigned to one of the two study groups within 12 hours of life. A computer code, managed by a clinician not involved in the clinical management, generated the random allocation.The randomisation, with unequal blocks, was created with StataCorp (2017 Stata Statistical Software: V.15. College Station, Texas, USA: StataCorp).

The intervention group (strict group—STG) had CGM active alarms for glycaemic values <10° and >90° percentile (3.44 mmol/L (62 mg/dL) and 7.78 mmol/L (140 mg/dL)),[12] while the control group (CLG) had alarms for standard glycaemic values (2.61 mmol/L (47 mg/dL) and 10 mmol/L (180 mg/dL)). In both arms, glucose infusion rate (GIR) was modulated using a 33% glucose solution administered by a second line added to infusions. In CLG GIR modulation followed the standard protocol; while in STG we used an experimental modulation protocol (box 1). However, in both groups, standard protocol was used if hyperglycaemia (>10 mmol/L (180 mg/dL)) or hypoglycaemia (<2.61 mmol/L (47 mg/dL)) occurred. Nutritional intakes and the feed advancement used in our unit are chosen following ESPGHAN (European Society for Paediatric Gastroenterology Hepatology and Nutrition) and other international recommendations (online supplemental file 1).[19 20] Glucose was infused both through 33% glucose infusion and through PN, and it was modulated using the former.

Box 1 Rate of glucose infusion for strict group based on continuous glucose monitoring system

Glucose between 3.44 mmol/L (62 mg/dL) (10° centile) and 7.78 mmol/L (140 mg/dL) (90° centile): no changes.

Glucose below 3.44 mmol/L (62 mg/dL):

- >2.94 mmol/L (53 mg/dL) (5° centile): increase rate of 33% glucose (v1=0.05 mL/hour or v2=0.1 mL/hour or v3=0.15 mL/hour).*
- <2.94 mmol/L (53 mg/dL) at first determination, or <3.44 mmol/L (62 mg/dL) after 2 hours post increase of rate: increase rate of 33% glucose (v1=0.1 mL/hour or v2=0.2 mL/hour or v3=0.3 mL/hour).*

Glucose over 7.78 mmol/L (140 mg/dL):

- <8.83 mmol/L (159 mg/dL) (95° centile): decrease rate of 33% glucose (v1=0.05 mL/hour or v2=0.1 mL/hour or v3=0.15 mL/hour).*
- >8.83 mmol/L (159 mg/dL) at first determination, or >7.78 mmol/L (140 mg/dL) after 2 hours post reduction of rate: decrease rate of 33% glucose (v1=0.1 mL/hour or v2=0.2 mL/hour or v3=0.3 mL/hour).*

It is possible to change rate of 33% glucose for a maximum one major or two minor changes every 24 hours.

*Use v1 if weight ≤1000 g; v2 if weight is between 1000 and 1500 g; v3 if weight is ≥1500 g.

The CGMS is composed of the Enlite sensor, the Guardian transmitter and the VEO monitor (by Medtronic Minimed Paradigm VEO) (online supplemental file 2).[12]

The CGM sensor was placed using a sterile technique on the neonate's thigh and was connected to the transmitter. In order to minimise the potential procedural stress and painand if the infant was not sedated for any other reason, 0.2 mL of sucrose 33% was orally administered before the procedure.

The CGM had to be maintained for at least 96 hours and until the end of the sensor's life (average time 130 hours). The monitor was calibrated every 8 hours using POC glucometer's (Medtronic Stat Strip Xpress) glycaemia value (GTX). CGMS monitors showed glycaemic values continuously and in RT.

If the sensor showed malfunction or needed to be replaced because of dislocation, only a single replacement was permitted.

At the end of the monitoring time, the recorded data were downloaded using the provided software. CGM's findings, together with the clinical data and information, were collected in a dedicated database protected by a password and accessible only by medical staff involved in the study.

The primary outcome was the number of severe dysglycaemic episodes (<2.61 mmol/L or >10 mmol/L (<47 mg/dL or >180 mg/dL)) in the intervention group versus the CLG, during the monitoring time. We considered an episode a period of dysglycaemia of at least 10 min.

Secondary outcomes included the time (%) spent in euglycaemia (between 2.61 and 10 mmol/L (47 mg/dL and 180 mg/dL)), the number and the duration of hypoglycaemia and hyperglycaemia episodes, and the absolute time spent in dysglycaemia. Mild and severe hypoglycaemic and hyperglycaemic ranges are defined as: mild hypoglycaemia (2.61–3.44 mmol/L (47–62 mg/dL)); mild hyperglycaemia (7.78–10 mmol/L (140–180 mg/dL)); severe hypoglycaemia (<2.61 mmol/L (47 mg/dL)) and severe hyperglycaemia (>10 mmol/L (180 mg/dL)).[12]

Clinical outcomes evaluated included early and late onset sepsis, antibiotics' courses, time of invasive and non-invasive ventilation, oxygen therapy, incidence of bronchopulmonary dysplasia at 36 weeks of postmenstrual age, use of steroids, grade III/ IV intraventricular haemorrhage (IVH), incidence of periventricular leucomalacia, hypotension and requirement of inotropic drugs, incidence of retinopathy of prematurity requiring treatment, necrotising enterocolitis (≥stage II according to Bell's criteria[21]), length of hospitalisation, and mortality at 28 days of life and at discharge.

All data were collected in the NICU of the Fondazione Policlinico Universitario Agostino Gemelli IRCCS Catholic University Hospital between October 2018 and September 2019.

Sample size and statistical analysis

Sample size was calculated using a VLBW population at risk of dysglycaemic episodes previously evaluated in our centre.[12] In this population, 1.2±0.4 (mean±SD) dysglycaemic episodes were detected in the first 72 hours of life. Assuming that strict glycaemic control in a similar population could reduce this

incidence by 33%, with an error α of 0.05 and a β of 0.1, and a power of 90%, the number of patients estimated was 23 neonates for each arm.

The statistical analysis was performed for each neonate who completed the study period of 96 hours. Continuous data are expressed as mean (SD) or median (IQR) as appropriate. Normality of continuous data was evaluated. The comparison of the continuous variables was performed using the t-test or the Wilcoxon rank-sum test depending on the distribution of the variable (respectively normal or non-normal). The dichotomous variables were reported as counts and percentage and analysed by X^2 test or Fisher's exact test.

The association between the glycaemic control and the dysglycaemia episodes is reported as relative risk (RR), calculated as ratio of the probability of normal glycaemia in the intervention (STG) group to the probability in the CLG.

The effectiveness of the intervention is reported as number needed to treat (NNT); it is the average number of patients who need to be treated to prevent one additional bad outcome and it is calculated as the inverse of the absolute risk reduction (inverse of the difference between the incidence of dysglycaemia in the STG and the incidence in the standard group).

The statistical analysis was performed using Stata/IC V.15.1 software for Windows.

RESULTS

A total of 63 neonates met the eligibility criteria during the study period. Among these, one had severe congenital skin alteration so he did not meet the inclusion criteria, parents declined to participate for seven infants, and seven were excluded because the CGMS was not available. The remaining 48 neonates were enrolled from October 2018 to September 2019. One baby in the STG group died in the first day of life. Forty-seven neonates completed the entire protocol (figure 1), 23 in STG and 24 in CLG. The two populations did not differ for any of the prenatal and perinatal data (table 1).

The overall mean GIR was similar during the study period between the two groups: 7.94±1.1 g/kg/day vs 7.98±0.92 g/kg/day (online supplemental files 3 and 4).

Our results show that the median number of severe episodes of dysglycaemia for every infant was significantly lower in the STG group compared with CLG: 1 (IQR 0–2) vs 3 (IQR 1–7); (p=0.005) (online supplemental file 5).

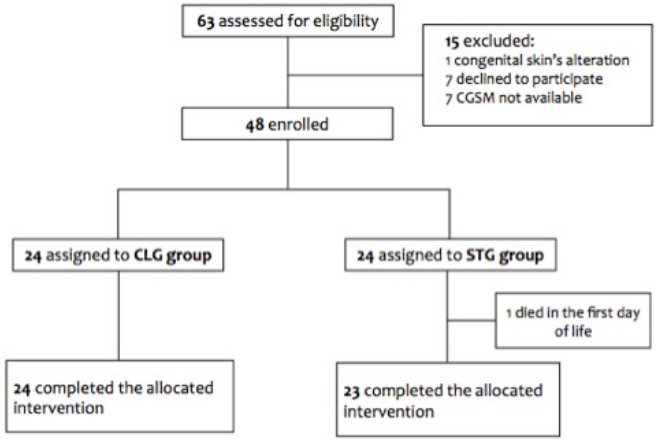

Figure 1 Trial profile—CONSORT flow diagram. CGMS, continuous glucose monitoring system; CLG, control group; CONSORT, Consolidated Standards of Reporting Trials; STG, strict group.

Table 1 Basic population details

Basic population details	STG (n=23)	CLG (n=24)	P value
Gestational age (weeks); mean (SD)	29 (2)	28(3)	0.50
Birth weight (g); mean (SD)	1002 (257)	984 (319)	0.83
Small for gestational age*; no (%)[20]	8 (35)	8 (33)	0.84
AED-ARED; no (%)[20]	10 (43)	9 (38)	0.90
Caesarean section; no (%)	21 (91)	20 (83)	0.70
Male; no (%)	13 (57)	16 (67)	0.68
Intrapartum antibiotics; no (%)	6 (26)	5 (21)	0.94
Antenatal steroids (any dose); no (%)	16 (70)	18 (75)	0.93
Endotracheal intubation in delivery room; no (%)	3 (13)	4 (17)	0.95
Non-invasive ventilation in delivery room; no (%)	18 (78)	20 (83)	0.94
Apgar 1; median (IQR)	7 (6–7.5)	7 (6–8)	0.50
Apgar 5; median (IQR)	9 (8–9)	9 (8–9)	0.90

*<10° centile according to growth charts used in the unit.
AED-ARED, absent end diastolic flow-absent reversed end diastolic flow; CLG, control group; STG, strict group.

Also, our results show a statistically significant difference in the number of infants with at least one episode of severe dysglycaemia between the two groups (12 vs 20; p=0.047).

The total mean time of monitoring was not different between the two groups: 7820 min (SD ±1065) vs 8114 min (SD ±799) for STG and CLG, respectively (p=0.29).

The infants managed using the strict protocol had a higher probability of having normal glycaemic values (between 2.61 mmol/L and 10 mmol/L (47 and 180 mg/dL)) than infants of the control group: RR 2.87 (95% CI 1.1 to 7.3). The NNT (calculated to avoid dysglycaemia episodes) is 3.2 (95% CI 1.8 to 16.6).

STG infants spent more time than CLG infants in euglycaemia: 100% (IQR 97–100) vs 98% (IQR 94–99), p=0.036.

Focusing on the time spent in 'mild' dysglycaemia, we found that it tended to be lower in the STG group: 560 min (IQR 285–1080) vs 973 min (IQR 539–1610) for the CLG group, p=0.07. Furthermore, the time spent in 'severe' dysglycaemia was 10 min (IQR 0–225) in the STG group, compared with 165 min (IQR 10–378) for the CLG group, p=0.066 (table 2).

Overall, considering all the episodes of severe hypoglycaemia and hyperglycaemia, in our population hypoglycaemia episodes had a median of 72.5 min (IQR 18.75–192.5), while hyperglycaemia episodes had a median of 590 min (IQR 122.5–1008).

The two groups were comparable for the short-term clinical outcomes (table 3).

Infants were also carefully monitored for signs of adverse events at sensor insertion sites, such as infection, irritation, subcutaneous haemorrhage and subcutaneous sensor wire breakage. The application of the sensor appeared to be safe and well tolerated (evaluated with the pain scale routinely used in our ward, that is the Neonatal Pain, Agitation and Sedation Scale). It did not interfere with nursing care. We needed to replace the sensor in two patients.

DISCUSSION

Our results show that, thanks to CGM-guided glucose infusion administration, it is possible to achieve a reduction of dysglycaemia episodes and increase the time spent in euglycaemia in high-risk infants.

Following the protocol of the study (box 1), we managed to obtain very tiny modification of glucose intake (for example, two minor changes correspond to a modification of about 1.5 g/kg/day of glucose intake).

CGM could have a great impact on optimising glycaemic control[22] and there is growing interest in using CGM devices

Table 2 Clinical outcomes (at discharge/death)

	STG (n=23)	CLG (n=24)	P value
Primary outcome			
Severe episodes; median (IQR)	1 (0–2)	3 (1–7)	0.005
Severe episodes (at least one); no (%)	12 (52)	20 (83)	0.047
Secondary outcomes			
Severe hypoglycaemia time*; median (IQR)	0 (0–35)	10 (0–130)	0.27
Severe hyperglycaemia time*; median (IQR)	0 (0–83)	0 (0–366)	0.32
Severe dysglycaemia time*; median (IQR)	10 (0–225)	165 (10–378)	0.066
Severe hypoglycaemia episodes; median (IQR)	0 (0–1)	1 (0–3)	0.16
Mean time* severe hypoglycaemia; median (IQR)	0 (0–30)	10 (0–23)	0.54
Severe hyperglycaemia episodes; median (IQR)	0 (0–1)	0 (0–3)	0.15
Mean time* severe hyperglycaemia; median (IQR)	0 (0–58)	0 (0–93)	0.55
Mild episodes; mean (SD)	11 (7.13)	15 (9.41)	0.11
Mild hypoglycaemia time*; median (IQR)	155 (20–368)	138 (28–333)	0.87
Mild hyperglycaemia time*; median (IQR)	290 (5–768)	565 (203–1248)	0.12
Mild dysglycaemia time*; median (IQR)	560 (285–1080)	973 (539–1610)	0.07
Mild hypoglycaemia episodes; median (IQR)	4 (1–8)	4 (1–8)	0.56
Mean time* mild hypoglycaemia; median (IQR)	40 (11–66)	27 (13–64)	0.84
Mild hyperglycaemia episodes; median (IQR)	4 (1–10)	5 (2–13)	0.52
Mean time* mild hyperglycaemia; median (IQR)	31 (3–93)	68 (50–157)	0.09
% time nomoglycaemia (2.61–10 mmol/L); median (IQR)	100 (97–100)	98 (94–99)	0.036
% time optimal glycaemia (3.44–7.78 mmol/L); median (IQR)	91 (84–95)	87 (70–92)	0.15
Period of monitoring*; mean (SD)	7820 (1065)	8114 (799)	0.29

*Time is expressed in minutes.
CLG, control group; STG, strict group.

in NICU to support the clinical management of VLBW neonates.[11 13 18 23–26] RT data on interstitial glucose levels provide information on glucose trends with the potential for earlier intervention and prevention of dysglycaemia.

The wealth of data now available from CGM makes it attractive for use in NICU where many physiological variables are measured continuously. Intensive care studies demonstrated that the time within a physiological target range is linked to better survival. The benefits in NICU may be greater: CGMS help increase minimal handling of the neonates and limit blood sampling. Furthermore, RT glucose monitoring has a potential impact in reducing dysglycaemia on the vulnerable developing brain.[27]

So far, studies have attempted to use CGMS to guide clinical management to support the targeting of glucose control in preterm infants. A single-centre feasibility study of the RT monitors demonstrated that percentage of time in target range (2.61–10 mmol/L (47–180 mg/dL)) was greater with CGM than POC (77% vs 59%, respectively) and percentage of time sensor glucose >10 mmol/L (180 mg/dL) was lower with CGM than POC (24% vs 40%, respectively). The CGM also detected clinically unsuspected episodes of hypoglycaemia.[28]

Galderisi *et al* demonstrated that compared with standard treatment, CGM-guided glucose titration and glucose administration using a proportional–integrative–derivative control algorithm can increase the time spent in an optimal glycaemia range defined as 4–7.99 mmol/L (72–144 mg/dL) and minimise glycaemic variability in infants born ≤32 weeks' gestation or birth weight ≤1500 g during the first week of life.[13]

The use of insulin infusion and its safety to control hyperglycaemia has been previously evaluated.[17 29] These findings showed an increase of hypoglycaemic events without improvement in predefined outcomes.[14 17] A recent randomised pilot study evaluated the feasibility of a closed-loop control, based on CGM in preterm infants (birth weight <1200 g), to guide insulin delivery to support glucose control. The findings of this study show that this method could be feasible for the optimisation of glucose control in extremely preterm infants in intensive care.[29]

In the current study, we demonstrated that CGM-guided glucose infusion administration improves glycaemic control in very preterm infants by achieving a reduction of the number of dysglycaemic episodes. We also demonstrated that the strict glycaemic control significantly increases time spent in euglycaemia (looking at the data, considering the mean time of monitoring, even 1% of the time corresponds to more than an hour). We did not observe any significant difference in the other secondary outcomes between the two study groups. However,

Table 3 Clinical outcomes (at discharge/death)

Outcomes	STG (n=23)	CLG (n=24)	P value
EOS; no (%)	0 (0)	0 (0)	/
LOS; no (%)	5 (22)	6 (25)	0.94
Atb cycles; median (IQR)	2 (1–2.5)	2 (1–3)	0.5
MV days; median (IQR)	0 (0–0.69)	0 (0–4.25)	0.7
NIV days; median (IQR)	10 (3.5–34)	12,5 (6–37.75)	0.66
O_2 therapy, days; median (IQR)	4 (0.04–8.9)	14 (0.8–30.5)	0.27
IVH; no (%)	1 (4)	5 (21)	0.21
PVL; no (%)	1 (4)	2 (8)	0.9
BPD; no (%)	5 (22)	9 (38)	0.39
Postnatal steroids; no (%)	3 (13)	2 (8)	0.96
ROP requiring treatment (anti-VEGF); no (%)	1 (4)	3 (13)	0.63
Hypotension; no (%)	3 (13)	7 (29)	0.32
Inotropic drugs; no (%)	4 (17)	7 (29)	0.54
NEC; no (%)	3 (13)	2 (8)	0.66
Surgery for NEC; no (%)	0 (0)	2 (8)	0.49
Length of stay; median (IQR)	56 (37–79)	54 (48–77)	0.71
Mortality at 28 days; no (%)	3 (13)	1 (4)	0.57
Mortality at discharge; no (%)	1 (4)	2 (8)	0.95

Atb, antibiotics; BPD, bronchopulmonary dysplasia; CLG, control group; EOS, early onset sepsis; IVH, intraventricular haemorrhage; LOS, late onset sepsis; MV, mechanical ventilation; NEC, necrotising enterocolitis; NIV, non-invasive ventilation; PVL, periventricular leucomalacia; ROP, retinopathy of prematurity; STG, strict group; VEGF, vascular endothelial growth factor.

we noted a reduction trend of the time spent in 'mild' and 'severe' dysglycaemia in the STG compared with CLG. As for the clinical outcomes, we underline a lower incidence of IVH in STG compared with CTG. Some studies found an association between the frequent alterations of glucose levels in preterm infants and the resultant changes in osmolarity and cerebral blood flow, possibly leading to development of IVH, given the fragility of these blood vessels.[30] Although our result is not statistically significant, taking into consideration the biological plausibility between hyperglycaemia and IVH, we cannot rule out the possibility of a statistically significant difference with a larger population. However, we are aware that, at present, we cannot deduce any clinical result given the fact that the sample size was not calculated with this aim.

Such results could have a clinical impact, since the glucose variability is associated with an increase of mortality and morbidity in VLBW infants.[31–35]

These data confirmed that the CGMS is a useful instrument to evaluate blood glucose levels in preterm infants.[31] Furthermore, our protocol for managing GIR based on blood glucose percentiles and guided by CGMS is safe, effective and simple to apply.

This new approach could represent a step-change in care: our data demonstrate how it would be possible to apply new effective protocols for managing GIR in high-risk infants and support further development of new systems of managing glycaemic control with CGMS and dextrose infusion as tools.

Moreover, CGMS and RT glucose evaluation could allow to overcome the current limits of the 'significant hypoglycaemia and hyperglycaemia' definition, correlating it to the glycaemic trend rather than to punctual values.[6 36 37]

The main strengths of this study are the focus on a selected population at high risk of dysglycaemia, the use of a new generation RT-CGM device previously tested in a similar neonatal population and the capability of maintenance of euglycaemia by using a simple protocol to modulate GIRs.

Compared with other studies, for STG we chose glycaemic thresholds based on a previously studied distribution of glycaemic values in a similar population.[12] Moreover, while other trials addressed intervention using different types of monitoring,[13] this is the first study using unblinded RT monitoring in both study groups. Furthermore, it is the first randomised study evaluating the feasibility of the use of CGM in preterm infants to guide GIRs with a simple protocol to support glucose control, without the need of adaptive computerised algorithms. This system appears to be a potential adjunct for targeting glucose control in preterm infants requiring intensive care.

The study's limitations include a small population and the single-centre study design. As a consequence, the secondary outcomes have to be interpreted with caution, since the study was not powered to detect any difference in them. A larger number of patients could have highlighted more differences, both in secondary endpoints and clinical outcomes.

Although present data are promising, future multicentre trials of a larger population are needed to confirm our data. Moreover, assessment of long-term clinical outcomes related to this form of glucose management in VLBW, especially in terms of neurodevelopment, should be studied. Indeed, we will evaluate this population of infants in follow-up studies.

CONCLUSION

We provide evidence that CGM, combined with a protocol for adjusting glucose infusion, can effectively reduce the episodes of dysglycaemia and increase the percentage of time spent in euglycaemia in VLBW infants receiving PN in the first week of life.

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Contributors AP conceptualised and designed the study, designed the data collection instruments, enrolled patients, collected data, analysed the data, contributed to the interpretation of the results, drafted the initial manuscript, and reviewed and revised the manuscript. ET conceptualised and designed the study, enrolled patients, contributed to the interpretation of the results, and reviewed and revised the manuscript. LG and RI enrolled patients and reviewed and revised the manuscript. AS designed the data collection instruments, enrolled patients, collected data, analysed the data and drafted the initial manuscript. MLP designed the data collection instruments, enrolled patients, collected data and drafted the initial manuscript. TP enrolled patients, collected data and drafted the initial manuscript. FC contributed to the interpretation of the results and reviewed and revised the manuscript. LM contributed to the interpretation of the results and critically revised the manuscript. GV contributed to the interpretation of the results and critically revised the manuscript. All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

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Patient consent for publication Not required.

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Data availability statement Data are available upon reasonable request. The data that support the findings of this study are available on request from the corresponding author AP. Reuse is not permitted.

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