Izabela Szymońska, Mateusz Jagła, Katarzyna Starzec, Katarzyna Hrnčiar, Przemko Kwinta

THE INCIDENCE OF HYPERGLYCAEMIA IN VERY LOW BIRTH WEIGHT PRETERM NEWBORNS. RESULTS OF A CONTINUOUS GLUCOSE MONITORING STUDY – PRELIMINARY REPORT*

CZĘSTOŚĆ WYSTĘPOWANIA HIPERGLIKEMII U NOWORODKÓW Z BARDZO MAŁĄ MASA URODZENIOWĄ. BADANIE Z WYKORZYSTANIEM SYSTEMU CIĄGŁEGO MONITOROWANIA GLUKOZY – DONIESIENIE WSTĘPNE

Chair of Pediatrics, Collegium Medicum, Jagiellonian University, Cracow, Poland

Abstract

Aim: *To determine the incidence of hyperglycaemia in very low birth weight preterm newborns. To assess risk factors in hyperglycemia and outcome in groups of children with and without clinically significant hyperglycaemia.*

Material and methods: *The prospective study included newborns with very low birth weight in whom the continuous glucose monitoring system was used for glucose measurements. A standardized hyperglycaemia treatment schedule was implemented and a uniform nutrition strategy introduced. The patients were divided into groups: group A –patients with under 5% of the readings over 150 mg/dL of glucose (control group), group B – patients with more than 5% of the readings over 150 mg/dL of glucose and under 5% of the readings over 180 mg/dL of glucose (mild hyperglycaemia), and group C – patients with over 5% of the readings >180 mg/dL or on insulin treatment (moderate or severe hyperglycaemia).*

Results: *63 patients were included in the study. Their mean gestational age was 27.7 weeks (SD: 2.4), the mean birth weight was 1059g (SD: 262 g). Hyperglycaemia was detected in 27 (42.9%), including mild hyperglycaemia in 19 (30.2%), and moderate or severe hyperglycaemia in 8 (12.7%) neonates. Lower gestational age ($p=0.02$) and higher CRIB II score ($p<0.01$) were positively associated with hyperglycaemia. Early-onset sepsis ($p<0.01$) was associated with higher glucose levels as well. A significantly higher mortality rate on the 28th day of life ($p = 0.02$), depending on the severity of hyperglycemia, was noted. No adverse effects related to the continuous glucose monitoring system were observed.*

Conclusions: *The study confirmed the usefulness and safety of the continuous glucose monitoring system in VLBW neonates. A continuous glucose monitoring system should be used in neonatal intensive care units as a standard method.*

Key words: continuous glucose monitoring, hyperglycaemia, praematurity, CGM

Streszczenie

Cel: *Określenie częstości występowania hiperglikemii w populacji noworodków przedwcześnie urodzonych z bardzo małą masą urodzeniową ciała. Ocena czynników związanych z występowaniem hiperglikemii. Ocena rokowania w grupach dzieci bez i z klinicznie istotną hiperglikemią.*

Materiał i metody: *Do prospektywnego badania włączono noworodki przedwcześnie urodzone z bardzo małą masą urodzeniową. Do pomiaru stężenia glukozy wykorzystano system ciągłego*

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monitorowania glikemii. Stosowano jednolitą strategię żywieniową i postępowanie terapeutyczne. Pacjentów podzielono na grupy: grupa A – dzieci, u których liczba pomiarów stężenia glukozy powyżej 150 mg/dl była mniejsza niż 5% wszystkich pomiarów (grupa kontrolna), grupa B – liczba pomiarów stężenia glukozy powyżej 150 mg/dl była >5%, ale liczba pomiarów glukozy >180 mg/dl była <5% wszystkich pomiarów (łagodna hiperglikemia), grupa C – liczba pomiarów powyżej 180 mg/dl wynosiła >5% lub dziecko wymagało leczenia insuliną (umiarkowana lub ciężka hiperglikemia)

Wyniki: *Badaniem objęto 63 dzieci urodzonych średnio w 27,7 tygodniu ciąży (SD: 2,4) ze średnią masą ciała 1059g (SD: 262g). Hiperglikemię stwierdzono u 27 (42,9%), w tym łagodną u 19 (30,2%), a ciężką lub umiarkowaną u 8 (12,7%) pacjentów. Niższy wiek płodowy (p=0,02), większa punktacja w skali Clinical Risk Index for Babies II (p<0,01) oraz częstsze występowanie posocznicy o wczesnym początku (p<0,01) były związane z wyższymi stężeniami glukozy. Oceniając rokowanie, zaobserwowano istotnie wyższą śmiertelność noworodków w 28 dobie życia (p=0,02) w zależności od stopnia ciężkości hiperglikemii. Nie obserwowano objawów niepożądanych związanych ze stosowaniem systemu ciągłego monitorowania glikemii*

Wnioski: *Ciągłe monitorowanie glikemii, dające możliwość jej skuteczniejszej kontroli u wcześniaków, powinno być rutynową procedurą diagnostyczną w oddziałach intensywnej terapii wcześniaka.*

Słowa kluczowe: ciągłe monitorowanie glukozy, hiperglikemia, wcześniactwo, CGM

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INTRODUCTION

Hyperglycaemia is one of the most prevalent metabolic conditions in very low birth weight preterm infants (VLBW). The pathogenesis of hyperglycaemia in preterm infants is complex. The prevalence and determinants of high glucose levels still remain unclear. Continuous parenteral glucose intake, immature altered metabolism [1], lack of suppression of endogenous glucose release and production in response to a parenteral glucose infusion [2-4], a limited amount of insulin-dependent tissue (fat and muscle), a limited insulin secretory response to glucose [5], and a multiplicity of stressful events (respiratory distress, surgery, pain, sepsis) are mentioned among the factors which may be relevant. Hyperglycaemia may be associated with death [8-8], intraventricular hemorrhage (IVH) [6, 9], late-onset bacterial infection [7], the retinopathy of prematurity (ROP) [10, 11], necrotizing enterocolitis (NEC) [7], and white matter reduction [8]. There is a lack of consensus regarding the threshold level defining hyperglycaemia in VLBW infants. The most common limits used for analyses are >8.3 mM/L (>150 mg/dL) [6, 8], and >10.0 mM/L (> 180 mg/dL) [7, 12].

The gold standard consists in determining the plasma glucose level by means of the laboratory enzymatic method. However, it involves repeated puncture for blood sampling and gives no continuous, real-time information about glycaemia and its trends. The incidence of hyperglycaemia in preterm infants based on the intermittent sampling method has been estimated between 25% and 75% [1, 13].

The continuous glucose monitoring (CGM) system is a diagnostic device which gives detailed data. It is proven that CGM has a good correlation with capillary glucose levels and is safe in newborns [14, 15]. It was used in previous studies but the data were blinded for clinicians. We used a CGM system as a diagnostic tool, offering real-time observation and intervention based on the readings.

AIM OF THE STUDY

The aim of this study was to investigate the incidence of hyperglycaemia in very low birth weight preterm newborns using real-time continuous glucose monitoring. Moreover, assessment of the risk factors of hyperglycemia was performed. The prospective analysis of primary and secondary outcomes in groups of children with and without clinically significant hyperglycaemia was also conducted. The study is part of the "Strict versus liberal glucose control in VLBW infant" research project.

MATERIAL AND METHODS

From January 2013 to September 2014 a single-centre prospective study was conducted at the Neonatal Intensive Care Unit of the Department of Pediatrics, Polish-American Children's Hospital, Jagiellonian University, a third level neonatal centre in Cracow, Poland.

Neonates were eligible for the study if they were born below 32 weeks of gestation, had less than 1500 g birth weight and were admitted to the unit during the first day of life. Exclusion criteria were: major congenital malformations, a diabetic mother, and suspicion of an inborn error of metabolism, perinatal trauma and asphyxia. The study protocol was approved by the Jagiellonian University Ethics Committee, and written informed consent was obtained from a parent of each infant.

For glucose measurements a continuous glucose monitoring system was used (Guardian Real-Time CGM®, Medtronic, Northridge, CA). The continuous glucose monitoring sensor (SofSensor®, Medtronic, Northridge, CA) was inserted into the subcutaneous tissue of the

lateral side of the thigh, from which measurements were recorded every 5 minutes for the first week of life. The CGM system was calibrated at least 3 times daily with a blood sample obtained from the radial or umbilical arterial lines infused only with a saline solution. The data from the CGM system, as well as calibration values were not blinded and were available for clinicians.

A uniform intervention protocol was used. The first-line approach for hyperglycaemia was to reduce the rate of glucose infusion by 1-2 mg/kg/min – the minimal glucose infusion could not be lower than 4 mg/kg/min. The second line approach for hyperglycaemia was the introduction of an intravenous insulin infusion (starting dose: 0.2 units/kg/h). The interventions were started when glucose levels were higher than 180 mg/dL or clinically significant glycosuria was noted. In the case when glucose concentration decreased below 70 mg/dL, the rate of glucose infusion was increased by 1-2 mg/kg/min. In case of symptomatic hypoglycaemia or glucose level below 46 mg/dL, bolus infusion of 10% dextrose – 2 ml/kg was immediately started. A uniform nutrition strategy was provided for all patients.

The incidence of hyperglycaemia defined as 150 mg/dL, 180 mg/dL, and 270 mg/dL and hypoglycaemia defined as 46 mg/dL and 70 mg/dL were investigated.

The data from CGM were downloaded on completion of the 7-day study period. Patients were classified into 3 groups: 1) group A: <5% of the total reading time of all the measurements was over 150 mg/dL of glucose (control group), 2) group B: >5% of the reading time was >150 mg/dL of glucose but the number of measurements over 180 mg/dl was <5% of the measurements overall (mild hyperglycaemia), and 3) group C: >5% of the total reading time was over 180 mg/dL of glucose, or patients were treated with insulin infusion (moderate or severe hyperglycaemia).

Mean daily glucose concentration, mean nutrition intake and outcomes were analyzed.

A retrospective analysis of hyperglycaemia risk factors was performed. Birth weight, gestational age, CRIB II score, SGA, antenatal steroid administration, placental abruption, early-onset sepsis, respiratory distress syndrome, and surfactant administration were included among the risk factors.

Moreover, a prospective analysis of outcomes in groups of children with and without clinically significant hyperglycaemia was conducted. The primary outcome was defined as mortality by the 28th day of life and death before 36 PMA. Secondary outcomes were as follows: the incidence of sepsis, intraventricular hemorrhage (IVH according to Papille classification[16]), patent ductus arteriosus (PDA) requiring treatment with ibuprofen or surgical ligation, necrotizing enterocolitis (NEC≥2 stage according to Bell classification [17]), periventricular leukomalacia (PVL according to deVries classification [18]), retinopathy of prematurity (ROP based on the International Committee for the Classification of Retinopathy of Prematurity [19]), bronchopulmonary dysplasia (BPD defined as oxygen dependency beyond 36 weeks of the postmenstrual age), and somatic growth at 36 weeks of the postmenstrual age.

Student t, $\chi 2$, ANOVA, Kruskal Wallis, and Mann-Whitney U, Cochran–Armitage tests were used to compare baseline and outcome variables, as appropriate. Next, different factors associated with hyperglycaemia in univariate analyses were entered as covariates for the logistic regression analysis. Logistic regression was used to estimate the odds ratios for hyperglycaemia among VLBW neonates. The results are presented as mean (±SD), number (percentage), or median (interquartile range), unless otherwise indicated. Probability values below 0.05 were considered statistically significant. MedCalc Statistical Software version 14.12.0 was used for statistical analysis (MedCalc Software bvba, Ostend, Belgium; http://www.medcalc.org; 2014).

RESULTS

Incidence of hyperglycaemia

A total of 102 334 glucose measurements were recorded by the continuous glucose monitoring system. This corresponds to 511 670 minutes, 8528 hours or 355 days of measurements, and represents a mean of 135.4 hours (range 52.5-164.8 h) for each patient.

Glucose levels >150 mg/dL occurred in 84.1% (n=53) of the infants, >180 mg/dL in 34.9% (n=22) of the infants, and >270 mg/dL in 4.8% (n=3) of the infants. The highest glucose concentration registered in our study was 302 mg/dL. Episodes of glucose level <70 mg/dL, were recorded 4003 times, which accounted for 3.9 % of all the measurements. Only 0.17% (169 measurements) of all the readings showed a glucose level of 46 mg/dL or lower and occurred in 13 patients.

Clinically significant periods of high glucose concentration were defined as 5% of all the readings per patient. Thirty six infants were included in Group A (<5% of reading time over 150 mg/dl), 19 infants in Group B (>5% of reading time over 150 mg/dl – mild hyperglycaemia) and 8 infants in Group C (>5% of reading time over 180 mg/dl or patients treated with insulin infusion – moderate or severe hyperglycaemia).

Glucose and Nutritional Data for Groups

Mean daily glucose concentration in groups is shown in figure 1. A significant difference between group A and groups B and C was found on day 3, 4, 5, and 7.

Mean daily fluid, glucose, proteins, and lipid intake in the groups observed are shown in figure 2. Statistically significant lower glucose intake was evident in group C on day 4, 5 and 6.

Six patients were treated with an insulin infusion (9.5% of the cohort). Two of them died on day four. None of the patients needed a continuous insulin infusion for a 24 hour period. According to CGM results, an intermittent insulin infusion was used (range 4-21 hours per day).

Risk factors for hyperglycaemia

The clinical characteristics of all the cohorts and statistical analysis of risk factors are given in the table I. Statistically significant factors, which were: gestational age, a CRIB II score and early-onset sepsis were included in the initial logistic regression model. Early-onset sepsis and a CRIB II

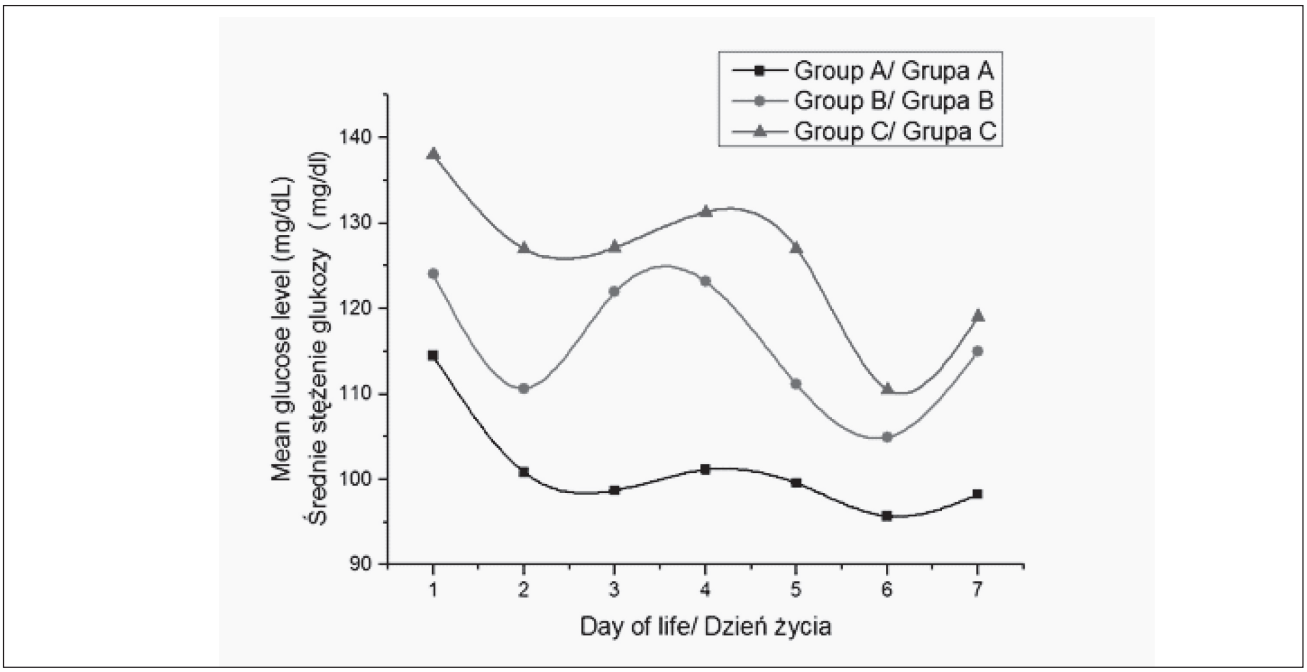

Fig. 1. Mean daily glucose concentration in observed groups (Kruskal Wallis test, day 3 p< 0.01; day 4 p<0.01; day 5 p<0.01, and day 7 p<0.03).

Ryc. 1. Średnie dzienne stężenie glukozy w badanych grupach (test Kruskal Wallis, dzień 3 p<0,01; dzień 4 p<0,01; dzień 5 p<0,01, dzień 7 p<0,03).

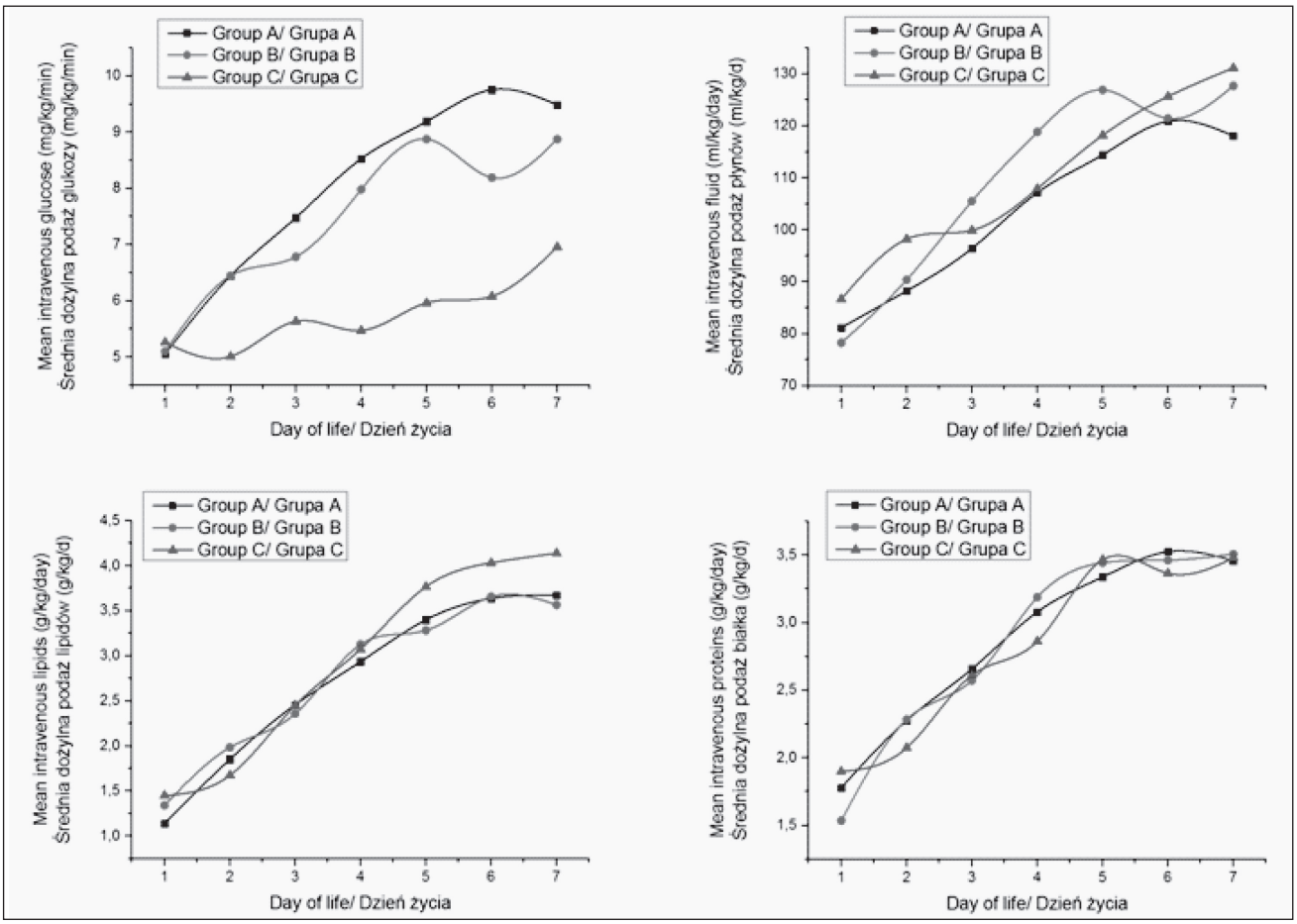

Fig. 2. Mean daily fluid, glucose, protein and lipid intake in groups (Kruskal Wallis test for intravenous fluid intake, p>0.05; ANOVA test for intravenous glucose at day 1, 2, 3, 7, lipid intake, protein intake, p>0.05; ANOVA test for intravenous glucose at day 4, 5, 6 p<0.01; p=0.04; p=0.02; respectively)

Ryc. 2. Średnia, dzienna podaż płynów, glukozy, białka oraz lipidów w grupach (test Kruskal Wallis dla dożylnej podaży glukozy, p>0,05; test ANOVA dla dożylnej podaży glukozy w dniach 1, 2, 3, 7, podaży lipidów, podaży białka, p>0,05; ANOVA test dla dożylnej podaży glukozy w dniach 4, 5, 6 odpowiednio: p<0,01; p=0,04; p=0,02)

Table I. Demographic and Clinical Characteristics of Patients.
Tabela I. Charakterystyka demograficzna i kliniczna pacjentów.

	All *Wszyscy*	**Group A** *Grupa A*	**Group B** *Grupa B*	**Group C** *Grupa C*	**p value** *wartość p*
Number of patients *Liczba pacjentów*	63	36	19	8	
Birth weight, g *Masa urodzeniowa, g*	1059.4±262,0	1160.0±192,0	917.5±225.0	944.1±414.1	0.65[a]
GA, wk Wiek płodowy, tyg.	27.7±2.4	28.4±1.9	26.8±2.5	26.2±3.3	**<0.02**[a]
CRIB II, score *Punktacja w skali CRIB II*	7 (5-10)	6.5 (4-8)	8 (6.5-11.5)	10 (6.5-13.5)	**<0.01**[b]
SGA *Noworodek za mały w stosunku do wieku płodowego*	8 (12.7%)	4 (11.1%)	4 (21.1%)	0	0.29[c]
Antenatal steroids *Podaż sterydów prenatalnie*	40 (63.5%)	23 (63.9%)	10 (52.6%)	7 (87.5%)	0.22[c]
Placental abruption *Przedwczesne odklejenie łożyska*	10 (15.9%)	3 (8.3%)	6 (31.6%)	1 (12.5%)	0.07[c]
EOS *Posocznica o wczesnym początku*	3 (4.8%)	0	0	3 (37.5%)	**<0.01**[c]
RDS *Zespół zaburzeń oddychania*	52 (82.5%)	27 (75.0%)	18 (94.7%)	7 (87.5%)	0.17[c]
Surfactant *Podanie surfaktantu*	36 (57.1%)	20 (55.6%)	12 (63.2%)	4 (50.0%)	0.78[c]

Data are number (%), mean (±SD) or median (IQR). P value: a is for one way ANOVA, b is for Kruskal Wallis, c is for χ2 test. GA: gestational age, CRIB II: Critical Risk Index for Babies II, RDS: Respiratory Distress Syndrome, EOS: early onset sepsis
Wyniki podano jako liczbę (%), średnią (±SD) lub medianę (rozstęp kwartylny). Wartość p: a – dla jednoczynnikowej analizy warinacji ANOVA, b – dla testu Kruskal Wallis, c – dla testu χ2. GA: wiek płodowy, CRIB II: skala Critical Risk Index for Babies II, RDS: zespół zaburzeń oddychania, EOS: posocznica o wczesnym początku.

score were positively associated with the risk of moderate/severe hyperglycaemia. A further model showed that only the CRIB II score was a statistically significant independent factor associated with mild hyperglycaemia (OR 1.45; 95% CI 1.16-1.83) and moderate/severe hyperglycaemia (OR 1.29; 95% CI 1.04-1.59). Although early-onset sepsis had a clear association with the increased risk of moderate/severe hyperglycaemia, there was a wide confidence interval and these effects did not reach statistical significance (OR 2.69; 95% CI 0.36-20.3).

Clinical outcome

Primary and secondary outcomes for groups are presented in table II. The tendency to increased mortality by the 28th day of life (p=0.09 for for χ^2 test) was observed. Moreover, a significant positive association with the severity of hyperglycaemia (p=0.02 for Cochran–Armitage test) was revealed. A higher incidence of IVH (p=0.09) in groups with mild and moderate/severe hyperglycaemia was noted. Other outcomes did not significantly differ between the groups.

DISCUSSION

Multiple studies by different authors [2, 4, 5, 6] have been performed to understand the pathophysiology and consequences of hyperglycaemia in VLBW infants. Nonetheless, no uniform definition of hyperglycaemia in VLBW infants has been accepted. Various treatment schedules for hyperglycaemia and different guidelines concerning parenteral nutrition and insulin therapy have been used.

Studies also differ in the methods used for blood sampling and the frequency of glucose measurements. Observations were mostly based on the intermittent blood glucose control. It is believed that even 50% [14] of glucose abnormalities could be undetected by discrete measurements. Only few [13, 14, 16] studies analyzed data from CGM, which avoids the error of underestimation. However, they were blinded for clinicians.

The "Strict versus liberal glucose control in VLBW infant" research project (Jagła M, Szymońska I, Starzec K, Hrnčiar K, Kwinta P) which has not yet been published, was a clinical trial where CGM was used as a diagnostic tool. The real-time glucose readings were unblinded. Clinicians' decisions were based on the readings. The purpose of this paper was to determine the incidence of hyperglycaemia in VLBW infants based on real-time glucose monitoring. The CGM system measured glucose level every 5 minutes, and the frequency of the readings resulted in quasi-continuous observation, similar to that of heart rate or blood saturation monitoring in NICU.

Table II. Primary and secondary outcomes for the study cohort.

Tabela II. Pierwotne i wtórne punkty końcowe w badanej grupie.

	Group A *Grupa A* (n = 36)	**Group B** *Grupa B* (n=19)	**Group C** *Grupa C* (n=8)	**p-value** *wartość p*
Death before 28 days *Zgon przed 28 dobą życia*	1 (2.8%)	2 (10.5%)	2 (25.0%)	**0.09**[b] **0.02**[c]
Death before 36 PMA *Zgon przed ukończeniem 36 tygodnia licząc od daty ostatniej miesiączki*	3 (8.3%)	2 (10.5%)	2 (25.0%)	0.39[b]
Any IVH *Krwawienie dokomorowe*	14 (38.9%)	13 (68.4%)	5 (62.5%)	**0.09**[b]
IVH III or IV *Stopień III lub IV krwawienia dokomorowego*	6 (16.67%)	2 (10.53%)	3 (37.5%)	0.23[b]
PVL *Leukomalacja okołokomorowa*	1 (2.8%)	0	0	0.75[b]
NEC ≥2 grade *Martwicze zapalenie jelit*	5 (13.9%)	0	0	0.72[b]
LOS *Posocznica o późnym początku*	16 (44.4%)	1 (5.3%)	2 (25.0%)	0.16[b]
ROP, all stage *Retinopatia wcześniaków, wszystkie stopnie*	18 (50.0%)	12 (63.2%)	3 (37.5%)	0.43[b]
ROP, stage 3 or 4 *Retinopatia wcześniaków, stopnie 3 lub 4*	8 (22.2%)	9 (31.8%)	2 (25.0%)	0.14[b]
BPD *Dysplazja oskrzelowo-płucna*	6 (16.7%)	7 (36.8%)	1 (12.5%)	0.18[b]
Hospital stay, days *Czas trwania hospitalizacji*	59.5±28.4	70.6 ± 26.6	58.3 ±51.2	0.18[a]
Weigh 36 weeks PMA *Masa ciała w wieku 36 tygodni liczonych od daty ostatniej miesiączki*	2383.9 ± 517.3	2086.3 ± 435.6	2384.7 ± 804.8	0.16[a]

Data are number (%), mean ±SD. P value: a is for Kruskal Wallis test, b is for χ2 test, c is for Cochran–Armitage test. IVH: intraventricular haemorrhage; PVL: periventricular leukomalacia; PDA: patent ductus arteriosus; LOS: late onset sepsis; ROP: retinopathy of prematurity; BPD: bronchopulmonary dysplasia; PMA: postmenstrual age.

Wyniki podano jako liczbę (%), średnią (±SD). Wartość p: a dla testu Kruskal Wallis, b dla testu χ2, c dla testu Cochran–Armitage. IVH: Krwawienie dokomorowe, PVL: leukomalacja okołokomorowa; PDA: przetrwały przewód tętniczy; LOS: posocznica o późnym początku; ROP: retinopatia wcześniaków; CLD: dysplazja oskrzelowo-płucna; PMA: wiek liczony od daty ostatniej miesiączki

In our study, the number of readings considered to be over any limits (150 mg/dL, 180 mg/dL) represented less than 10% of all the registered measurements. The data analyzed revealed more patients with at least one measurement over 150 mg/dL compared to studies which used the intermittent blood sampling method (84.1% of infants vs 57%) [6]. However, it was similar to Iglesias et al., when blinded data from CGM were analyzed (88% of infants) [14].

Similar results were presented with respect to the percentage of patients with at least one glucose reading >180 mg/dL, (38% vs 34.9%) [14]. Moreover, in the study published by Beardsall et al. [13], (also analyzing blinded data from CGM), the incidence of glucose readings over 180 mg/dl was even higher (57% of the patients). It revealed that many preterm infants reached the limits of 150 mg/dL and 180 mg/dL if no interference was used. However, due to more effective intervention based on real-time monitoring, the duration of time over the accepted glucose level was significantly shorter in our study compared to Iglesias et al. (mean 20.3 h vs 3.15 hours) [14].

The CGM readings available in real-time resulted in significant differences in the percentage of patients who exceeded glucose levels >270 mg/dL (4.8 % vs Beardsall et al. 23%) [13]. The highest glucose level in our study was 302 mg/dL, when even 9% of the patients reached levels over 360 mg/dL in Beardsall et al. study [13].

The lower accepted glucose limit in our study was defined as 70 mg/dL. It was designed to avoid episodes of hypoglycemia, and as a result, both the thresholds of 70 mg/dL and 47 mg/dL were occasionally exceeded.

CGM being used as a diagnostic tool shows the need to modify the definition of hyperglycaemia. It became

obvious that crossing the accepted limits of glucose without the considerable duration of hyperglycaemia is not appropriate. We accepted the value of 5% of the time of all the measurements per patient as a clinically significant duration of high glucose concentration (Group A, B, C). More than 30.1% of the neonates were classified as group B, and 12.7 % as group C (the difference in the mean daily glucose concentration was significant).

Lower gestational age and higher points on the CRIB II score had a strong association with higher glucose levels and the longer duration of hyperglycaemia, which correspond with former data [11, 20, 21]. The study also confirmed that early-onset sepsis occurs most often in infants with higher glucose levels. The relation had previously been found in late-onset sepsis[7] and fungal infection [22].

It had previously been observed that hyperglycemia occurring on the first days of life is a risk factor of death [6, 8]. Similarly, in our study significant positive association between mortality by the 28th day of life and the severity of hyperglycaemia was confirmed. What is more, in groups with a clinically significant hyperglycaemia a higher risk of intraventricular hemorrhage was noted. This indirectly indicates the strong correlation between hyperglycaemia, the prevalence of IVH and mortality.

Mean daily intravenous fluid, proteins and lipids were similar in the groups. The difference in mean daily intravenous glucose intake between groups was statistically relevant. It has been shown that group C had a much lower glucose supply. Despite this, infants in group C reached the highest glucose levels. It confirms that glucose values are not directly dependent on parenteral glucose infusion.

Insulin therapy was administrated to fewer than 10% of all the newborns, compared to other studies, where 64% [17], 36% [16], and 31.6% [14] newborns received an insulin infusion. It was probably a consequence of the availability of real-time readings, which allowed clinicians to modify the rate of the glucose infusion. This suggests that glucose levels could be partially controlled by the modification of glucose infusion.

The controversy about insulin treatment of hyperglycaemia has been previously reported. Insulin admission could have a positive effect on somatic growth and the avoidance of ROP, but also increases the number of episodes of hypoglycemia and mortality [16, 17]. In our study infants in all the groups achieved similar somatic growth at 36 weeks of postmenstrual age and the incidence of ROP was the same. Although the balance of risk and benefits of insulin treatment proposed in our study seems to be appropriate, the first-line approach to hyperglycaemia treatment has to be addressed in further studies.

CGM is one of the invasive methods of blood glucose monitoring due to sensor insertion in subcutaneous tissue. However, the study confirmed the safety of using the system in VLBW neonates [14, 15]. No adverse effects related to the insertion or maintenance of subcutaneous sensors were noted. We observed no infection, bleeding or skin damage. The monitoring period does not impair nursing care. No discomfort was noted among the neonates.

The study had limitations regarding its statistical power, due to the small sample size. These are preliminary results in the "Strict versus liberal glucose control in VLBW infants" project, a survival analysis will be performed at the end of the study.

The definition of hyperglycaemia has been one of the crucial controversies in neonatology. The prevalence of single readings >150 mg/dL suggests that this threshold is too rigorous for preterm neonates, should be considered as a norm and requires no treatment. This study suggests that hyperglycaemia should be defined not only as the value of glucose level but also as the duration of this state over a defined threshold . Adequately designed studies are necessary to investigate the means of glucose variability and determine the duration of hyperglycaemia for primary and secondary outcomes, especially for the development of white matter in the brain.

CGM is not a guarantee of glucose homeostasis itself. However, it is a great clinical diagnostic tool which allows better glucose control, avoidance of hypoglycemia and extreme high glucose levels.

CONCLUSIONS

The study confirmed the usefulness and safety of the continuous glucose monitoring system in VLBW neonates. The continuous glucose monitoring system should be used in neonatal intensive care units as a standard method.

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Author for correspondence:
Izabela Szymońska
Department of Pathology and Intensive Care of Newborn,
Clinic of Children's Diseases, Chair of Paediatrics,
Jagiellonian University Medical College
265 Wielicka Street, 30-663 Krakow
tel. (12)658-02-56
e-mail: i.szymonska@gmail.com