

Treatment of Severe Hyperglycemia in Extremely Preterm Infants Using Continuous Subcutaneous Insulin Therapy

Boettger M et al. CSII in Extremely Preterm Infants

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What is already known on this topic?

Hyperglycemia is common in preterm infants and can affect long-term outcomes, especially regarding the neurological outcome. However, there are no treatment guidelines and there are a lot of controversies. Insulin is mostly administered via continuous intravenous infusion in preterm infants. Continuous subcutaneous insulin infusion in preterm infants is only described in a few case reports and clinical research papers.

What this study adds?

This study adds clinical expertise in the application of CSII in extremely preterm infants. The comparison of CSII and intravenously given Insulin in preterm infants allows to draw conclusions on the feasibility and dose control of CSII in preterm infants. To our knowledge it is the largest, described cohort of extremely preterm infants receiving CSII.

Abstract

Background: Hyperglycemia in preterm infants is usually treated with adjustment of glucose intake and, if persistent, with continuous insulin infusion. However, hypoglycemia is a well-known complication of iv insulin treatment. The aim of our study was to evaluate the feasibility of continuous subcutaneous insulin infusion (CSII) in extremely preterm infants.

Methods and material: Clinical data from 15 extremely premature infants (<28 weeks of gestation) undergoing CSII treatment for severe hyperglycemia at the NICU were included. Blood glucose levels during CSII as well as the nutritional intake and insulin intake were sampled. Data were analyzed and compared to a control group of very preterm infants receiving iv insulin therapy.

Results: Normoglycemia rates were best in the iv insulin-cohort (50.7% vs 15.6%). Hypoglycemia was very rare in both groups (0.4%; 0.0%).

CSII therapy might require higher insulin doses compared to continuous iv therapy.

Discussion: Subcutaneous Insulin therapy in extremely preterm infants is feasible, regarding the prevention of hypoglycemia. However, dose control needs to be improved.

Conclusion: The results justify further model validation and clinical trial research to explore a model-based protocol and the use of CSII.

Keywords: Continuous subcutaneous insulin infusion, extremely preterm infants, hyperglycemia

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Background

Regarding long-term neurocognitive development, prevention of hypo- and hyperglycemia plays a major role in the care of premature infants (PI). Persistent hyperglycemia occurs mostly in very low birthweight infants (VLBW) in the first days to weeks of life [1,2]. There is a negative correlation between gestational age (GA), birth weight, and the occurrence of hyperglycemic episodes [1]. In this respect, an isolated blood glucose (BG) level >10 mmol/L within the first 28 days of life in VLBW is associated with a more than 2-fold increase in 28-day mortality [3]. Furthermore, hyperglycemia within the first 24 hours of life is associated with reduction in brain white matter structure on MRI [4].

Thresholds for managing hyperglycemia vary considerably across clinical settings [5,6,7,8,9]. Due to varying definitions and methodological differences for blood glucose level assessment, the incidence of hyperglycemia in studies varies between 40-80% [1,3,10,11]. The prevalence of hyperglycemia is highest at the end of the second week of life with approximately 30% of preterm infants below 1500g presenting with BG levels > 10 mmol/l [10,11].

Management of hyperglycemia starts with the adjustment of glucose intake considering reduction to a basic requirement of 5-6 g/kg/d.

Insulin treatment has been introduced using continuous iv infusion [3,12,13,14,15]. However, increased catheter-associated infections have been described with intravenous treatment [2]. In addition, the use of iv insulin infusion involves the fear of a resulting, iatrogenic hypoglycemia. Although subcutaneous insulin therapy is regarded as a standard treatment of diabetes management in the pediatric population, very few data exist for using CSII in neonatal hyperglycemia. Available data are limited to a few studies in connection with neonatal diabetes mellitus [16,17], case reports, or "close loop" monitoring in neonates [6-8]. Hence, there is a gap in knowledge, which might offer benefit.

In the neonatal intensive care unit (NICU) of the University of Oldenburg, subcutaneous insulin treatment in the management of hyperglycemia of extremely preterm infants was introduced as part of standard care since 2015. The aim of this study is to review the management of hyperglycemia following a standard CSII protocol in view of feasibility and safety. Data are compared with a cohort of preterm infants, treated for hyperglycemia within the first weeks of life using iv insulin from the NICU of Christchurch, New Zealand.

Methods

In a retrospective multi center observational study 15 extremely preterm infant, receiving CSII treatment for severe hyperglycemia in the first weeks of life during the period 01/01/2015 to 01/04/2021, were identified. All infants were inborn patients treated at the level 3 NICU of the

University of Oldenburg. Data on patient characteristics, BG test results, insulin medication, enteral nutritional intake, and administration of parenteral iv infusion and individual drug medication were collected from patient records. Enteral glucose was supplied either as breast milk or preterm formula. For breast milk, a carbohydrate content of 70mg per liter was estimated. The carbohydrate content of preterm formula was calculated according to the manufacturer's instructions.

All BG measurements were performed by rapid Accu-Chek blood glucose test (Roche Diabetes Care, Inc, Indianapolis, Indiana, USA). The definition of hyper- and hypo- glycemia, as well as the therapeutic intervention in the management of transient hyperglycemia, followed the local NICU guideline: Hypoglycemia: < 4 mmol/l, Life-threatening hypoglycemia: < 2.6 mmol/l, Normoglycemia: 4 - 10 mmol/l, Hyperglycemia: > 10 mmol/l. For BG values > 16.65 mmol/l measured repeated within 12 hours, reduction of parenteral glucose infusion rate in 1-1.5 g/kg/d steps to a minimum of 5-6 mg/kg/h is done first. The indication for continuous insulin therapy is given if BG values >16.65 mmol/l persist over a period of 12 hours despite adjustment of the iv glucose rate to a minimum of 5-6 g/kg/d. According to our guideline, the initial dosing of CSII is 0.01-0.05 IU/kg/h, increased in small increments to a maximum rate of 0.1 IU/kg/h following the measured BG values. Insulin dosing gets re-evaluated and modified at the bedside with each BG measurement (3 hourly). A BG level between 8.3-11.2 mmol/L (150 - 200 mg/dL) is the goal BG target range during CSII.

All preterm infants used an Accu-Chek Combo insulin pump (Roche Diabetes Care, Inc, Indianapolis, Indiana, USA) with rapid-acting (2-5 hour action duration) Humalog insulin (Eli Lilly Co, Indianapolis, Indiana, USA). Because the insulin pumps were not designed for use in preterm infants, which means the standard insulin concentration of 100 IU/ml would have limited delivery in premature infants. Therefore, the insulin was diluted 1/10 to achieve a concentration of 10 IU/ml. The subcutaneous needle is placed at the thigh of the patients and is routinely changed every 48-72 hours according to the guidelines. The insulin in the pump is routinely changed every 7 days.

Results were compared with a retrospective iv insulin treated cohort consisting of preterm infants, consisting of 22 VPI at the NICU in Christchurch, New Zealand between 2005-2009. Analogous to the procedure in Oldenburg, a reduction in glucose intake was done first in the corresponding study period in the case of persistent hyperglycemia. With two values above 10 mmol/L, intravenous insulin therapy with 0.05 IU/kg/h was started. In the course, a fixed adjustment was made depending on the BG value.

For statistical analysis, descriptive tests were used. The distribution of values was non-Gaussian. Statistical analyses were processed using statistical software (IBM Corp. Released 2019. IBM SPSS Statistics for Macintosh, version 26.0. Armonk, NY: IBM Corp).

Ethics approval to conduct this study was obtained from the Medical Ethics Committee of the University of Oldenburg (No.: 2021-024)

Results:

Patient characteristics are presented in Table 1. The n=15 VPI presented with a median birth-weight of 620 g and 24 weeks (IQR: 24+0 – 24+6) gestational age. CSII was initiated in median at 77 hours of life. The median duration of insulin therapy using CSII was 191 hours in the cohort. A total of 2736 hours of insulin therapy by CSII and 803 glucose readings were included. No major complications requiring treatment occurred. Local redness at needle insertion site was observed twice, and both healed spontaneously.

The iv-cohort is composed of n=22 preterm infants, 7 male, who received continuous iv insulin in the NICU at the Christchurch Women's Hospital, New Zealand. Median gestational age is 27 weeks (IQR: 26-27 GA) with median birth weight of 840 grams (IQR: 800-900g). Median duration of therapy is 86 hours (IQR: 32.5-184 hours). Table 1 depicts patient and therapeutic characteristics of both cohorts. Table 1 lists key delivery and outcome glycemia results for both cohorts. For the Oldenburg CSII cohort, the starting dose used is a minimum of 0.002 IU and a maximum of 0.102 IU/h/kg, with a median of 0.014 IU/h/kg (0.036-0.050 IU/h/kg). The minimum insulin intake in this cohort ranges from 0.002 to 0.051 IU/h/KG, spanning 0.049 IU/h/kg body weight. The maximum insulin dosage ranges from 0.011 to 0.181 IU/h/kg. A total of 40% (6 of n=15 VPI) of patients received insulin doses above the maximum recommended dose of 0.1 IU/h/kg (Figure 1), where all infants had highly variable administration rates. The interquartile range of insulin intake of the n=15 preterm infants from 0.02 - 0.05 IU/kg/h illustrates a high variability of the insulin dose used around the median of 0.02 IU/h/kg. In 3 VPI (20%; n=15), and the starting dose was below the recommended minimum of 0.01 IU/h/kg at baseline. In contrast, 6 of the n=15 VPI (40%) received an insulin supply above the recommended maximum of 0.1 IU/h/kg. The median insulin intake for the entire duration of therapy was below the possible recommended maximum starting dose of 0.05 IU/h/kg in 11 of the n=15 preterm infants.

The n=22 patients in the comparison group receiving iv insulin as a continuous insulin infusion had a median insulin dose of 0.03 IU/h/kg (Table 1). Insulin delivery rates had a higher median value, but similar range and IQR. Glucose administration was similar between the two cohorts. The evaluation of BG using CSII is based on the percentage of measured values in a defined range of normo-, hypo- and hyperglycemia. Only values measured during CSII insulin administration (> 0.0 IU/kg/h) were analysed. The percentages refer to the number of glucose readings of the individual n=15 patients. Figure 2 shows the percentages of individual patients results. In 10 of the 15 infants of the CSII cohort, contrary to expectations, a greater proportion of BG readings (58.8% - 100%) were above the defined reference range. In 5 preterm infants (33%) of this cohort (n=15), 50% to a maximum of 55% of the blood glucose readings were within the reference range. The maximum proportion of normoglycemia for each preterm infant considered individually is not very high at 55%. This outcome becomes clearer when considering all 803 glucose readings. Overall, across the CSII cohort, only 34.5% were between 4.0 - 10.0 mmol/l and only 13.2% between 4.0 - 8.0 mmol/l. Results and time in the normoglycemic range were relatively much higher for the iv insulin treated cohort (Table 1).

Discussion:

Severe hyperglycemia in extremely preterm infants is associated with numerous comorbidities into adulthood [4,8,18,19]. This outcome highlights the need for adequate therapy, which is faced due to the metabolic instability, functional insufficiency of compensating mechanism during the first weeks of life of extremely preterm infants [1,2,3,11]. The causes of dysregulation of glucose metabolism in preterm infants are diverse and include inadequate insulin production, low glycogen stores, and possible insulin resistance [7]. In addition, treatment of hyperglycemia with continuous iv insulin is difficult and requires close monitoring to avoid associated hypoglycemia. Hyperglycemia has been shown as the first sign of cerebral hemorrhage (IVH) and at the same time being attributed to its severity development [24]. As early as 1986, Ostertag et al. provided evidence extremely preterm infants could benefit from insulin pump therapy [25]. Previous findings provide evidence for lower glucose fluctuations due to insulin pump therapy with continuous glucose measurement, compared to continuous intravenous insulin administration [6,8].

In this study, 15 extremely preterm infants who received insulin subcutaneously via an insulin pump were studied. During the therapy period of more than 2700 hours, no local or systemic infections requiring treatment were observed. Furthermore, only one severe hypoglycemia was observed in more than 800 blood glucose measurements. Thus, the therapeutic use of subcutaneous insulin therapy in VPI might can be considered safe. However, in this study no CGM was used and thus hypoglycemia might be undetected.

The preterm infants in the CSII cohort and a comparator iv insulin cohort received similar insulin administration rates (CSII: 0.02 IU/h/kg; iv insulin: 0.03 IU/h/kg). However, the iv insulin cohort had a significantly higher proportion of normoglycemia (13.2%; 50.9%). Thus, the glycaemic control of the CSII cohort appears inadequate at similar insulin rates. However, the birth weight, as well as the gestational age of the CSII cohort are lower than the iv cohort. The results suggest the different kinetics of iv insulin versus sc insulin therapy, and particularly the potential for sc insulin losses, may explain the differences. Hence, the results suggest CSII in these cohorts may require a higher insulin dose, especially at start of the treatment, compared to iv insulin.

In the cohort studied, the median starting CSII insulin dose was within the in-house recommended range of 0.01-0.05 IU/h/kg. However, there was marked variability. The median value also corresponds to the dosage of insulin used in previous studies with a comparable question [9,26]. Compared with the cohort of continuous intravenous insulin delivery, the insulin rate of the CSII cohort is lower, even

though sc insulin losses may reduce its impact. This difference may also be attributed to differences in protocol between the units and a different level of acceptance regarding safe insulin dosing levels. The "hesitant" use of insulin contrasts with the high blood glucose values before the start of therapy and the high proportion of hyperglycemia during therapy. The reason for this issue could be the risk associated with hypoglycemia and a desire to avoid this outcome, which is certainly of high priority for preterm infants. However, to achieve continuous normoglycemia, adequate insulin dosing is essential. Moreover, persistent hyperglycemia (>180 mg/dl or 10 mmol/l) is also associated with worse outcome in preterm infants [13,27]. However, the lack of treatment recommendations using CSII makes adequate glycaemic control difficult. Avoiding hyperglycemia by means of adequate insulin delivery should be as high a priority as avoiding hypoglycemia.

In the n=15 preterm infants studied, adequate glycaemic control could not be achieved using a CSII with the insulin rates used. Overall, this study is a comparison of cohorts with differences in sample number, gestational age, and birth weight. Nevertheless, descriptive comparisons can be made because the number of glucose measurements and the total duration of insulin administration are similar. The importance of adequate insulin dosing is evident when considering the high proportion of hyperglycemia in the cohort studied. Severe hyperglycemia is associated with worse outcome in preterm infants [27]. For example, Kao et al. demonstrated a significant association between hyperglycemia (mean 7-day glucose >180 mg/dl or 10 mmol/l) and the occurrence of necrotizing enterocolitis (NEC) II°-III° [27]. In addition, hyperglycemia >8mmol/l in extremely preterm infants seems to be associated with delayed motor development and lower intelligence quotients at 6.5 years of age. Insulin therapy, on the other hand, appears to have no effect on either outcome. [28]. Current data suggest model-based insulin administration could improve therapy management. STAR GRYPHON is a metabolic model that already improves the control of continuous iv insulin therapy, considering factors such as enteral and parenteral glucose intake, weight and age. In the NICU in Christchurch, New Zealand, it has been used in clinical practice for some time [29]. In a recent study, Zhou et al. demonstrated model-based subcutaneous insulin therapy may allow for better control to achieve the goal of normoglycemia more rapidly and consistently [30].

The small number of cases in the study limits the conclusions which may be drawn from this analysis. Furthermore, the iv insulin cohort comparator is not randomized nor matched and was born around ten years before the CSII Group. In the last ten years there were a lot of changes in neonatology, which might affect the outcome as well. The CSII cohort received insulin in neonatal centres with different in-hospital standards and protocols. The IV treatment protocol had for example a lower treatment threshold, which has to be considered when looking at the results. In addition, the preterm infants in the iv insulin treated Christchurch cohort had a higher median gestational age and birth weight and a higher case load. Due to the small number of cases the calculation of p-values (p=0.05) to compare continuous non-parametric groups of values was waived. However, the differences and similarities in glycaemic outcomes allow conclusions to be drawn on the safety and potential efficacy of CSII in these cohorts and the need to better account for differences in insulin kinetics between delivery routes.

Summary:

Overall, the comparison of the two cohorts allows an indication of inadequate glycaemic control and insulin rates in the CSII cohort. This study shows CSII in extremely preterm infants is a feasible method but, compared with the retrospective iv insulin treated cohort, the current insulin regime leads to an insufficient control of hyperglycemia. In terms of hypoglycemia as well as local infections, CSII in extremely preterm infants appears quite safe. However, in view of different kinetics compared to iv therapy, there is still considerable potential for improvement in dosing. CSII requires higher dosing of insulin compared to intravenously administered insulin. Ideally, the mode of administration should be model-based to best account for inter- and intra-patient variability in kinetics and dynamics of insulin action. Randomized studies with an adequate number of cases are necessary once safe effective treatment protocols can be established.

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Table 1: Cohorts and demographic data for the CSII (Oldenburg, Germany) cohort and the iv insulin treatment cohort (Christchurch, New Zealand). Data are shown as median value and (range) or (IQR) as shown.

	CSII Cohort (Oldenburg)	iv Cohort (Christchurch)
n patients (n male)	15 (8)	22 (7)
Total hours of Treatment	2736	2946
Amount of blood glucose measurements	833	902
Duration of insulin application, hours [IQR]	191 [127-249]	86 [32.5-184]
Gestational age*, weeks [IQR]	24 [24-27]	27 [26-27]
Body weight*, gram [IQR]	720 [570-735]	840 [800-900]
Postnatal age**, days [IQR]	3 [1-5]	3 [1-7]
BG measurement interval, hours [IQR]	3.3 [2.9-3.9]	3.4 [2.8-3.9]
Insulin rates, IU/kg/h [IQR]	0.02 [0.02-0.05]	0.03 [0.02-0.05]
Total glucose input, mg/kg/min [IQR]	8.0 [6.8-9.6]	8.5 [5.5-9.2]
Blood glucose median [IQR]	11.2 [9.9-12.5]	7.9 [6.6-9.2]
Median % blood glucose between 4.0 – 8.0 mmol/L [IQR] (Mean)	15.6 [5.6-21.1] (13.2)	50.3 [42.1-66.3] (50.9)
Median % blood glucose > 8.0 mmol/L [IQR] (Mean)	62.8 [50.0-77.5] (65.0)	8.1 [4.9-21.4] (17.2)
Median % blood glucose < 4.0 mmol/L [IQR] (Mean)	0.0 [0.0-1.3] (0.5)	0.4 [0.0-3.0] (2.1)
Median % blood glucose < 2.0 mmol/L [IQR] (Mean)	0.0 [0.0-0.0] (0.1)	0.0 [0.0-0.0] (0.1)
Number of patients with blood glucose level < 2,6 mmol/L	1	1

* at birth

** at the start of insulin treatment

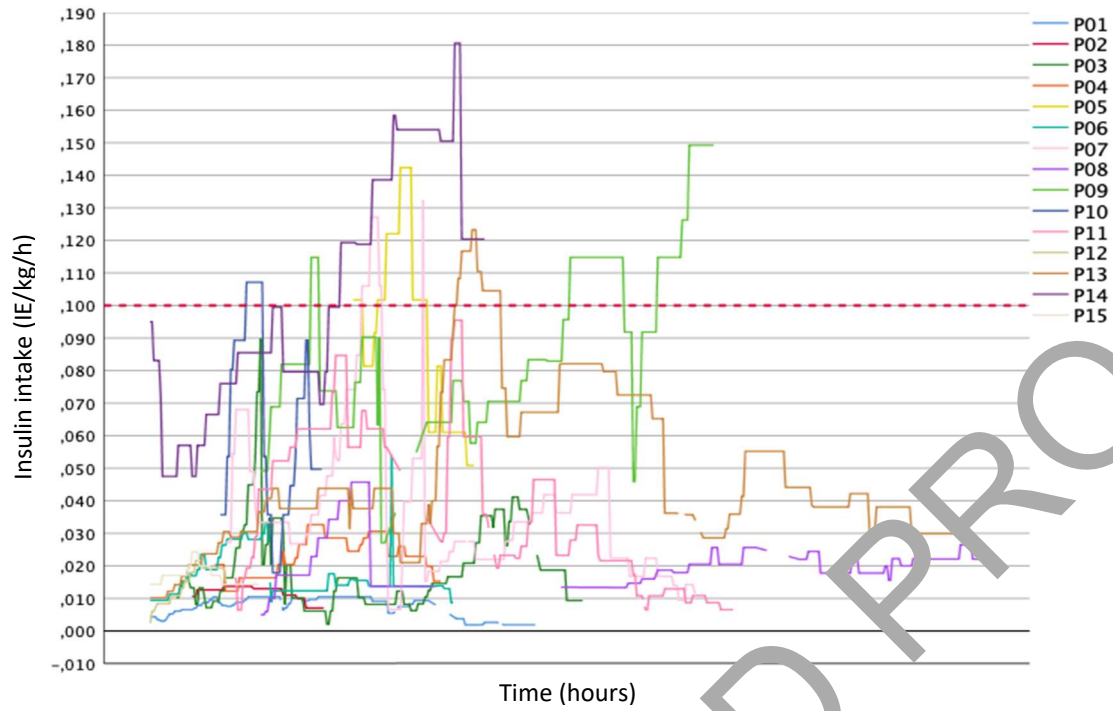


Figure 1: Insulin intake of VPI (n= 15) suffering from persistent hyperglycemia

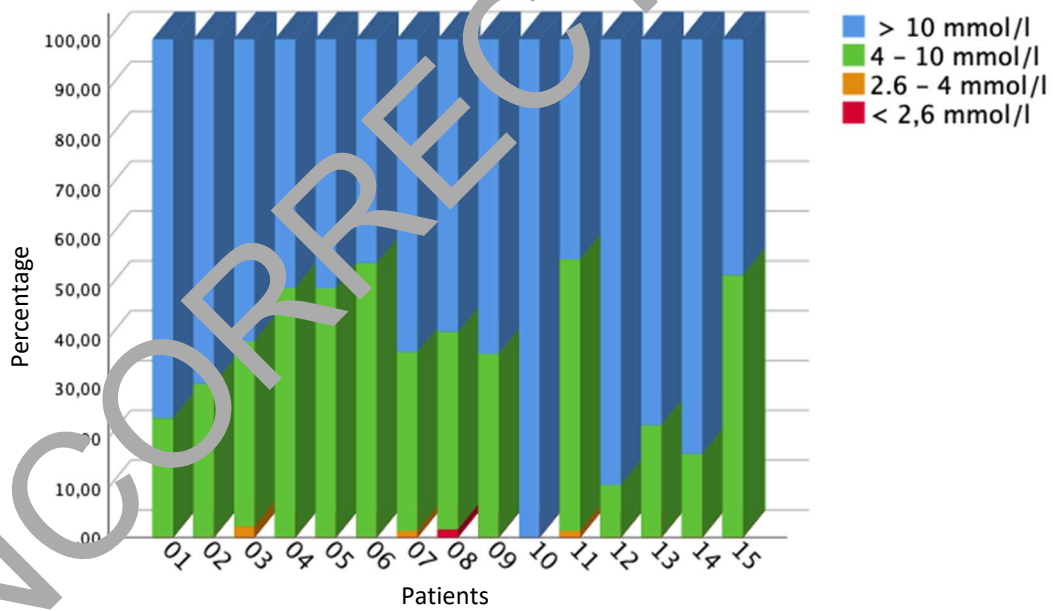


Figure 2. Percentage of glucose measured in plasma for each of the n=15 preterm infants