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Efficacy and Safety of a Tight Glucose Control Protocol in Critically Ill Term Neonates

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Key Words
Pediatric intensive care unit · Hyperglycemia · Insulin · Infant · Protocol

Abstract
Background: A large single-center randomized trial showed that treating hyperglycemia in critically ill children improved outcome, despite an increased incidence of hypoglycemia, especially in infants. ***Objectives:*** We evaluated the efficacy and incidence of hypoglycemia using a tight glucose protocol in critically ill term neonates. ***Methods:*** Term hyperglycemic (>8 mmol·l^{-1}; >144 mg·dl^{-1}) neonates treated with a tight glucose protocol during a 3.5-year period in a tertiary pediatric intensive care unit were retrospectively analyzed. ***Results:*** Seventy-three term hyperglycemic neonates [age 0 days (0–6), weight 3.2 ± 0.8 kg, PRISM 16 (11–20)] were included for analysis. Eighteen neonates died (25%). The initial mean (range) glucose level was 11.1 mmol·l^{-1} [9.6–15.2; 200 mg·dl^{-1} (173–274)], and normoglycemia (<8 mmol·l^{-1}; <144 mg·dl^{-1}) was reached within 5.3 h (1–25) with an overall treatment duration of 27 h (10–57). Seven hypoglycemic incidents (5 times ≤2.2 mmol·l^{-1}; 40 mg·dl^{-1}, and 2 times <1.7 mmol·l^{-1}; 31 mg·dl^{-1}) occurred in 5 (6.7%) infants, without severe clinical signs. Three hypoglycemic incidents were directly explained due to a protocol violation. One hypoglycemic incident occurred with the onset of sepsis, while no apparent cause was identified for three hypoglycemic incidents. ***Conclusions:*** Our glucose protocol was effective, but hypoglycemia occurred more frequently than in older children reported previously. Potential differences in glucose and insulin metabolism in term neonates appear to justify additional safety approaches, while awaiting further studies assessing the benefits of tight glucose protocols in this population. Meanwhile, we have decreased the initial insulin starting doses in our protocol.

Introduction

The acute stress response during critical illness causes hyperglycemia, which is associated with increased morbidity and mortality in critically ill adults, children, and neonates [1]. Although optimal glucose levels have not been established for any age group, it is becoming more evident that a worse outcome is independently associated with duration of hyperglycemia, peak glucose levels, increased glucose variability, and occurrence of hypoglycemia [2]. A tight glucose regimen with insulin therapy improved outcome in critically ill children [3], despite the occurrence of hypoglycemia [≤2.2 mmol·l^{-1} (40 mg·dl^{-1})]

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and severe hypoglycemia [≤1.7 mmol·l^{-1} (31 mg·dl^{-1})] in 25 and 5% of the children, predominantly (>80%) in infants [3]. A study with very low birth weight neonates with early insulin therapy showed an increased incidence of hypoglycemia (29 vs. 17%) and parenchymal abnormalities detected with cranial ultrasound in those treated with insulin, and was discontinued early on the grounds of futility [4].

Young age has long been recognized as a risk factor for developing hypoglycemia [5]. Furthermore, although duration and degree of hypoglycemia are important variables that have not been elucidated, the developing brain is susceptible to hypoglycemia and it may result in permanent damage [6, 7].

Glucose control protocols designed to maintain normoglycemia while minimizing glucose variability and hypoglycemic incidents are therefore of the essence in this population. Simple model-based computer-assisted or nurse-driven protocols have been reported in critically ill adults [8, 9] and children [10–12]. To date, no studies have shown feasibility and safety of these protocols specifically in critically ill newborn infants. Therefore, we evaluated the efficacy (time to achieve normoglycemia, duration of therapy) and safety (hypoglycemic incidents, protocol violations) of a tight glucose protocol in hyperglycemic term neonates less than 28 days old.

Patients and Methods

Patients

The Pediatric Intensive Care Unit (PICU) at Erasmus MC – Sophia Children's Hospital, Rotterdam, The Netherlands, is a 34-bed mixed ICU. Term neonates less than 28 days old, admitted to our PICU from January 2006 to September 2009, and treated with our tight glucose protocol were retrospectively evaluated.

Insulin Protocol

Term neonates received glucose according to our protocol (4–6 mg·kg^{-1}·min^{-1}) and were treated with a step-wise nurse-driven glucose control protocol which was published previously [12]. Briefly, neonates with sepsis, multiple organ failure, and/or receiving mechanical ventilation were treated after two consecutive blood glucose levels of >8 mmol·l^{-1} (>145 mg·dl^{-1}) within 1 h. Depending on the blood glucose level at the start of treatment, insulin was started at a dose ranging from 20 to 50 mIU·kg^{-1}·h^{-1}. Thereafter, the nurse was allowed to adjust the insulin rate according to the nurse-driven step-wise protocol up to a rate of 200 mIU·kg^{-1}·h^{-1}, after which the attending physician needed to be consulted. Blood glucose levels were checked hourly until the target range [4–8 mmol·l^{-1} (72–145 mg·dl^{-1})] was achieved for three consecutive measurements, after which measurements were performed every 3 h. Insulin therapy was stopped at any time according to clearly defined criteria in the protocol (fig. 1) [12].

Blood Glucose Analysis and Definitions

Blood glucose measurements were obtained by the nurses as soon as possible after admission from indwelling arterial catheters or from a capillary puncture, and measured on a blood gas analyzer (ABL 625; Radiometer, Copenhagen, Denmark) or a point-of-care bedside system (HemoCue AB, Sweden).

Normoglycemia was defined as blood glucose levels between 4 and 8 mmol·l^{-1} (72–145 mg·dl^{-1}). Time to reach normoglycemia was defined as the time from start of insulin therapy until the first blood glucose level <8 mmol·l^{-1} (<145 mg·dl^{-1}). Hypoglycemia was defined as blood glucose ≤2.2 mmol·l^{-1} (≤40 mg·dl^{-1}). Severe hypoglycemia was defined as blood glucose <1.7 mmol·l^{-1} (<31 mg·dl^{-1}) [3]. Signs of hypoglycemia were defined as mild (sweating, agitation, lethargy), severe [hemodynamic deterioration, neurological deteriorations (convulsions, coma)] or death. Measurements showing blood glucose levels <2.6 mmol·l^{-1} (47 mg·dl^{-1}) or >15 mmol·l^{-1} (272 mg·dl^{-1}) were repeated immediately on the blood gas analyzer. Neonates with blood glucose levels <2.6 (47 mg·dl^{-1}) were given a bolus of dextrose 10% 5 ml·kg^{-1} over 10 min.

Data Collection

Patients were assessed by the Pediatric Risk of Mortality (PRISM) score [13], which is a validated measure of the severity of multiple organ dysfunction in PICUs. Hypoglycemic incidents were recorded and analyzed for protocol violations. Based on our previous evaluation of the glucose protocol in children [12], we focused on two types of protocol violations (incorrect insulin starting dose, inadequate insulin adjustment/discontinuation).

Statistical Analysis

Data are presented as medians with interquartile ranges, unless otherwise specified. Statistical significance was considered at $p < 0.05$. Comparisons between neonates with and without hypoglycemia were made with the Mann-Whitney U test. Data were analyzed using a standard analysis software program (SPSS version 17.0 for Windows, SPSS, Chicago, Ill., USA). The study was approved by the Medical Ethics Committee of Erasmus Medical Center, and was registered in the Dutch trial register (www.trialregister.nl. registration number NTR2400).

Results

Patients

In the 44-month period, 4,919 children were admitted to our PICU, of whom 383 children (7.8%; age 4.9 year; 0–18) were treated for hyperglycemia. In total, 799 (16.2%) were neonates less than 28 days old, of whom 73 [9.1%; age 0 days (0–6), weight 3.2 ± 0.8 kg] were treated with the nurse-driven glucose control protocol. Their characteristics are shown in table 1. Overall mortality was high (25%) in the hyperglycemic neonates diagnosed with various medical and surgical diagnoses (table 2).

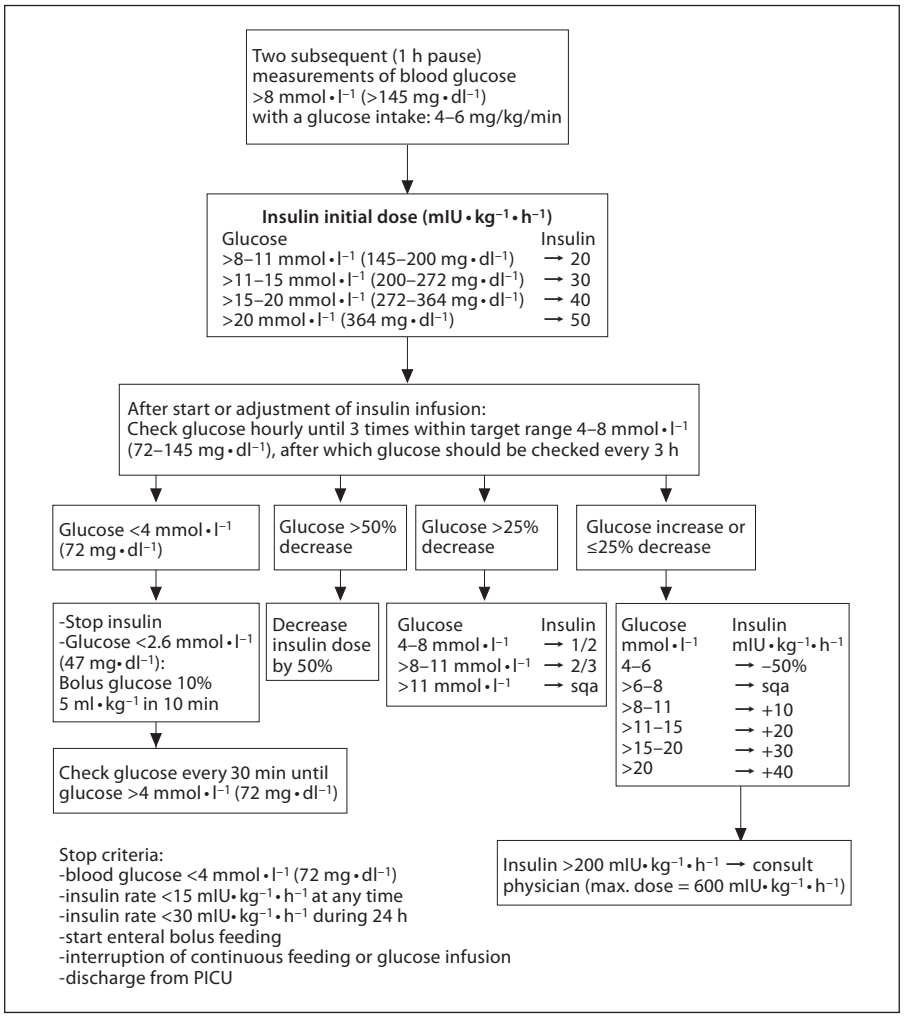

Fig. 1. Original and evaluated step-wise nurse-driven glucose control protocol for neonates less than 28 days old.

Table 1. Characteristics of neonates (0–28 days) treated according to glucose control protocol

	Normoglycemic (n = 68)	Hypoglycemic (n = 5)	All neonates (n = 73)	p value
Male:female	40:28	2:3	42:31	0.41
Age on admission to PICU, days	0 (0–5)	1 (0–21)	0 (0–6)	0.38
Mean weight ± SD, kg	3.2 ± 0.8	3.0 ± 0.5	3.2 ± 0.8	0.31
PRISM III	15 (12–22)	10 (5–12)	14 (11–20)	0.02
Glucocorticoids, n	40 (59%)	2 (40%)	42 (58%)	0.41
Mean glucose intake ± SD, mg·kg^{-1}·min^{-1}	4.7 ± 2.4	5.0 ± 1.1	4.7 ± 2.3	0.37
Time to start insulin infusion after first hyperglycemic incident, h	5.8 (2.5–11)	9.3 (2.3–25.4)	5.8 (2.5–11.0)	0.53
Time to achieve normoglycemia, h	5.3 (2.6–8.0)	6.1 (3.7–10.1)	5.3 (2.7–8.5)	0.40
Length of stay, days	15.5 (6.3–29.3)	7.0 (4.5–30.0)	15.0 (6.5–29.5)	0.54
Glucose level at start of insulin therapy, mmol·l^{-1}	11.2 (9.6–15.4)	10.8 (9.6–11.7)	11.1 (9.6–15.2)	0.49
Initial insulin dose, mIU·kg^{-1}·h^{-1}	20 (20–30)	20 (15–20)	20 (20–30)	0.13
Maximum insulin dose, mIU·kg^{-1}·h^{-1}	50 (30–88)	60 (45–75)	0 (30–80)	0.49
Duration of insulin therapy, h	26 (10–56)	33 (13–33)	27 (10–57)	0.37
Mortality, n	17 (27%)	1 (20%)	18 (25%)	0.75

Values are medians with IQR in parentheses, unless otherwise depicted; p values for normoglycemic vs. hypoglycemic neonates.

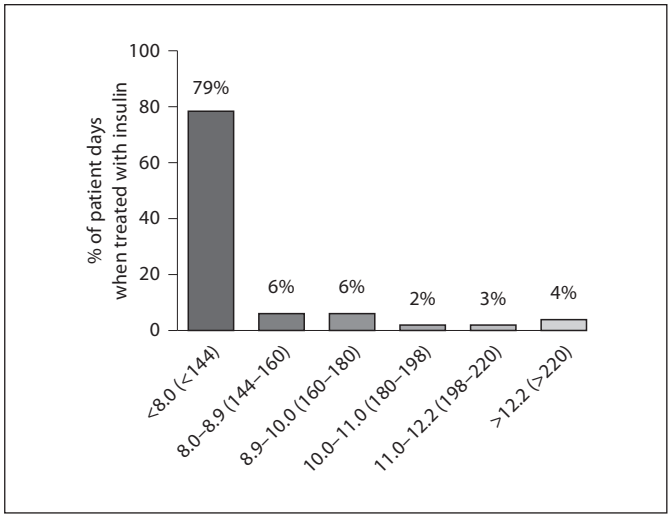

Fig. 2. Efficacy of the tight glucose control protocol in neonates treated with insulin showing the highest blood glucose readings in mmol·l^{-1} (mg·dl^{-1}) per day after start of the insulin therapy in percentage of patient days.

Table 2. Diagnoses of neonates treated according to glucose control protocol

	n
Surgical	
Non-ECMO	
Congenital diaphragmatic hernia	18
Congenital heart defect	7
Congenital abdominal malformation	10
Congenital pulmonary malformation	2
(Post-)Necrotizing enterocolitis	1
ECMO	
Congenital diaphragmatic hernia	9
Meconium aspiration	8
Persistent pulmonary hypertension	5
Congenital heart defect	1
Medical	
Infection	
Viral bronchiolitis	3
Meningitis	1
Sepsis	1
Meconium aspiration	1
Persistent pulmonary hypertension	3
Other	3

ECMO = Extracorporeal membrane oxygenation.

Intake

Overall glucose intake was 4.7 ± 2.3 mg·kg^{-1}·min^{-1} and not different in the neonates who developed hypoglycemia (table 1). At start of the insulin therapy, 5 neonates received full continuous enteral feeding, 37 received full parenteral nutrition with amino acids (Primene; Baxter Inc., Utrecht, The Netherlands) and lipids (Intralipid; Fresenius Kabi Inc., Utrecht, The Netherlands), and 4 were receiving combined (par)enteral nutrition. Thirty-three patients received no nutrients other than parenteral glucose.

Glucose Control Protocol

Insulin treatment was initiated 5.8 h (1–38) after the first episode of hyperglycemia [12.5 ± 4.1 mmol·l^{-1} (225 ± 74 mg·dl^{-1})]. The initial insulin starting dose was 20 mIU·kg^{-1}·h^{-1} (10–100), the maximum dose reached was 50 mIU·kg^{-1}·h^{-1} (20–450). We recorded a total of 196 patient days of insulin therapy, of whom 79.1% had daily blood glucose levels of <8.0 mmol·l^{-1} (<144 mg·dl^{-1}) (fig. 2). Normoglycemia was reached within 12 h of initiating insulin therapy in 65 neonates (90.3%), and the median time to reach normoglycemia was 5.3 h (1–25). One infant died before reaching the glucose target range. The overall duration of insulin therapy was 27 h (1–308), while 50 (68.5%) of the neonates were treated less than 48 h and only 12 (15.1%) neonates received insulin for >72 h.

Hypoglycemic Incidents and Protocol Violations

Episodes of moderate hypoglycemia occurred in 3 (4.1%) neonates and severe hypoglycemia occurred in 2 (2.7%) neonates, without any severe clinical signs. Four neonates were recorded as being pale and lethargic. The intervention with a bolus of glucose after insulin infusion was stopped was sufficient to treat the hypoglycemic incidents. One (20%) hypoglycemic infant died several days later due to portal vein thrombosis and acute liver failure after a Kasai procedure for biliary atresia. In the group who did not develop hypoglycemia, 17 (27%) neonates died. Blood glucose levels, age, glucocorticoid therapy, and clinical diagnoses at initiation of insulin therapy, dose and duration of insulin therapy, and time to achieve normoglycemia did not differ between hypoglycemic and non-hypoglycemic neonates (table 1). Hypoglycemia occurred twice in the 2 neonates with severe hypoglycemia, although severe hypoglycemia occurred no more than once in these neonates. Thus, a total of 5 hypoglycemic and 2 severe hypoglycemic incidents were recorded. The hypoglycemic incidents occurred at day 2 (1–5) of admission at the age of 4 days (1–30), 8 h (2–13) after initiation of insulin therapy.

Of these 7 hypoglycemic incidents, no apparent cause could be identified in three incidents. In retrospect, 1 hypoglycemic infant was diagnosed with sepsis within several hours after the hypoglycemic incident. Three protocol violations were identified which could have been responsible for the (severe) hypoglycemic incidents. In 2 neonates, insulin was decreased too late or not at all after plasma glucose levels dropped, whereas in 1 infant insulin was not discontinued according to the protocol.

In the 73 neonates receiving insulin, 31 protocol violations were identified at the initiation of insulin therapy, which were not associated with the hypoglycemic incidents. The starting dose of insulin was below protocol recommendations in 26 (34.7%) neonates and above protocol recommendations in 3 (4%) neonates. In 2 patients, the start of insulin should have been cancelled as the blood glucose was <8 mmol·l^{-1} immediately prior to the start of the insulin treatment.

Discussion

This is the first evaluation of the efficacy and safety of a tight glucose protocol specifically in critically ill term neonates. Consistent with previous evaluations of tight glucose protocols in older children [10–12], we showed that our nurse-driven glucose control protocol achieved normoglycemia within 5.3 h and in 90% of the neonates within 12 h and 79.1% of daily blood glucose levels of <8.0 mmol·l^{-1} (<144 mg·dl^{-1}). Remarkably, the target ranges were achieved while a large proportion (34.7%) of the insulin starting doses were below protocol recommendation. Furthermore, overall treatment duration was short, and it is not clear whether these neonates could have benefited from the tight glucose regimen.

While hyperglycemia is associated with a poor outcome in neonates [14–16], outcome studies of tight glucose protocols have not focused specifically on this population. Additionally, no mechanistic studies have explored the effects of hyperglycemia or insulin therapy in neonates. The principal cause of cellular and organ system failure in critical illness hyperglycemia is glucose overload resulting in excessive generation of oxygen radicals, which leads to mitochondrial dysfunction, increased generation of inflammatory cytokines, and disturbed energy metabolism [17]. Insulin therapy has been shown to protect the function and structure of the mitochondrial compartment in adults and children [18, 19]. It is not likely that there will be substantial differences in the mechanistic effects of hyperglycemia or insulin therapy on the glucose toxicity in infants. Therefore, despite the lack of beneficial results in outcome studies, potential benefits of insulin therapy in the infant population should not be ignored.

However, we recognize the 7 (severe) hypoglycemic incidents in 5 neonates (6.7%). Using a treatment algorithm in critically ill older children (by us and others), the reported incidence of hypoglycemia was 0–4% [10–12]. As the timeframe of the evaluation was similar for the older children without any hypoglycemic incidents [12] as for the infants in the present study, neither the protocol implementation, nor the experience working with the protocol by nursing staff and physicians, explains this difference. So, it appears that neonates are more susceptible to hypoglycemia following insulin administration.

Although three hypoglycemic incidents were explained by protocol violations, three hypoglycemic incidents occurred without apparent cause and one occurred in the onset of sepsis. Furthermore, in 2 neonates, hypoglycemia occurred twice. These observations allow us to speculate that neonates indeed are a specific and vulnerable age group in the PICU. Possibly the etiology in these neonates is different from the 'regular' insulin-resistance-induced critical illness hyperglycemia. For instance, in the pediatric population the initial phase of sepsis can cause insulin deficiency, rather than resistance [20]. Additionally, high parenteral glucose intake can, independent of insulin resistance, produce hyperglycemia. Under such circumstances, insulin infusion would decrease plasma glucose levels faster than under insulin resistant conditions. Furthermore, neonates lack the precise control of glucose homeostasis as they undergo major changes in glucose and insulin metabolism. Glycogen stores are low and glucose homeostasis primarily depends on gluconeogenesis, partially explaining why young age itself is a risk factor for developing hypoglycemia [5]. Furthermore, a transformation in β-cell population, due to a transient wave of apoptosis and repopulation, causes a wide variation of insulin secretory capacities in newborn neonates [21]. Moreover, hyperinsulinemic euglycemic clamp studies have shown that infants have greater peripheral glucose utilization [22] than older children [23]. Insulin receptors in infants are higher in number as well as affinity, partially explaining this increased sensitivity [24]. Additionally, it has recently been shown that there exists a developmental change in peripheral insulin signaling [25]. Although reduced contents of glucose transporters (GLUT) 1 and 4 were found, the proximal insulin signaling proteins (IR-β,

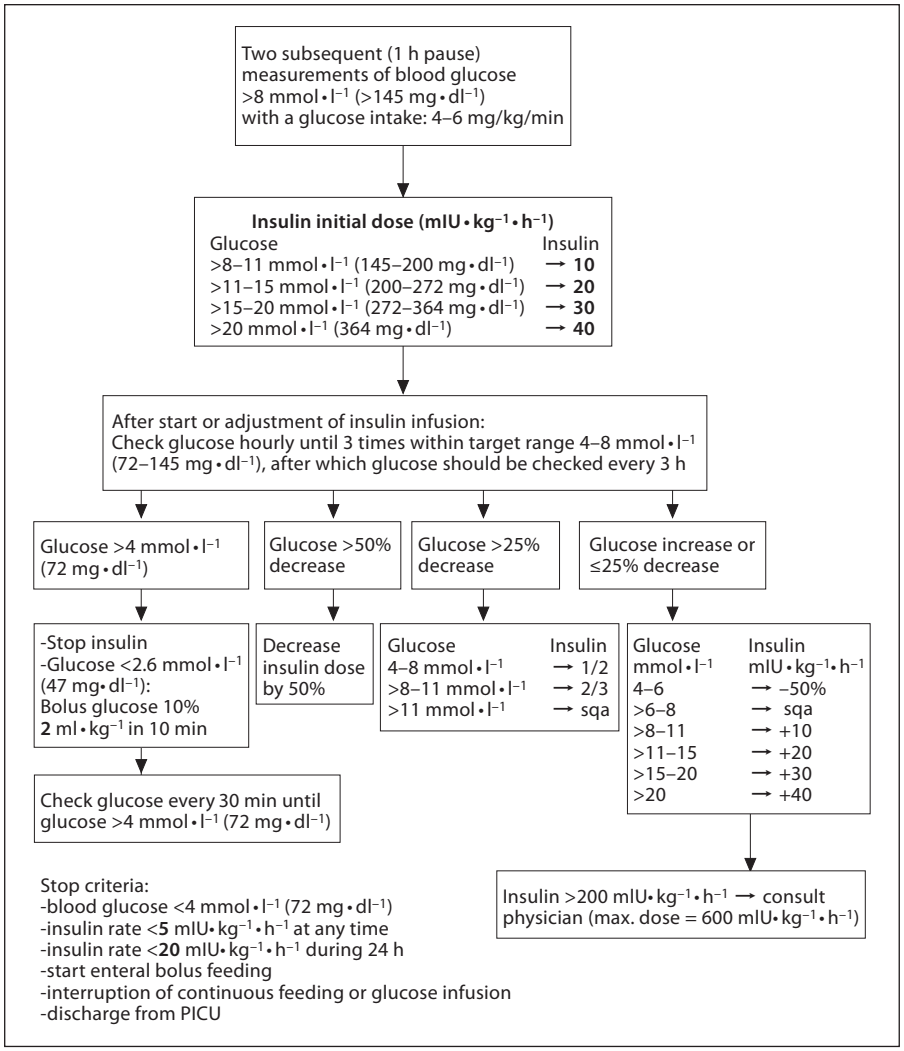

Fig. 3. Adjusted step-wise nurse-driven glucose control protocol for neonates less than 28 days old, based on the present study.

IRS-1 and Akt) were increased in muscle of neonatal baboons [25]. These wide variations in the ability of glucose production, insulin secretory capacity, and insulin sensitivity might at least partially explain the differences from older children and adults. Furthermore, it has been shown that β-cell dysfunction instead of, or in addition to, insulin resistance might play a major role in hyperglycemia during pediatric critical illness [20]. Whether this is also true in neonates is unknown. This suggests that when insulin therapy is considered in critically ill neonates, increased awareness is needed. With the results of the present study, we have adjusted the protocol on our PICU for infants less than 28 days old, such that the initial insulin starting doses decreased by 10 mIU·kg^{-1}·h^{-1} and the minimum insulin dose as stop criteria (fig. 3).

Our study has limitations. It is an observational study. It adds insight to the safety and effectivity of tight glucose protocols for critically ill neonates, but it was not designed to show whether outcome improved with our tight glucose protocol. We further acknowledge that our glucose target range was higher than that of Vlasselaers et al. [3], which could at least partially explain the difference in hypoglycemic incidents. However, as the ideal target range of tight glucose regimens still needs to be established, less strict protocols might be sensible.

We conclude that neonates can be treated with a nurse-driven glucose protocol, as target ranges were met, and overall treatment was short. However, hypoglycemia occurred more frequently in neonates than in older children, alerting us that this is a vulnerable population where additional safety approaches are warranted. Fu-

ture studies assessing the outcome of a tight glucose regimen in the infant population, and addressing approaches which will help prevent hypoglycemia, are of utmost importance. It should be emphasized that currently no evidence of the beneficial effect insulin therapy in neonates exists, and that insulin is a drug with potential serious side effects that should be used with care. Meanwhile, we will evaluate our adjusted protocol (fig. 3) and engage in a long-term follow-up of the neonates.

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Disclosure Statement

No conflict of interest reported.

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