Tight Glycemic Control in the Pediatric Intensive Care Unit

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Abstract

Keywords

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- ▶ stress hyperglycemia
- ▶ hypoglycemia

Hyperglycemia is a common complication in critically ill, nondiabetic children. Four large pediatric randomized controlled trials of tight glycemic control (TGC) have been conducted to date with contradicting results. This review will highlight the design and outcomes of these trials and other relevant studies to provide an overview of the advantages and disadvantages of TGC for different populations at risk of hyperglycemia along with future directions for research.

Stress Hyperglycemia in Critically Ill Children

Hyperglycemia is a common complication in critically ill, nondiabetic children that is thought to be caused by both increased gluconeogenesis and increased insulin resistance as a result of a surge of counter-regulatory hormones during critical illness.^{1–5} The stress response is characterized by a surge in cortisol and catecholamine levels that correlate with the severity of illness.⁶ The increased cortisol levels stimulate hepatic gluconeogenesis and inhibit glucose uptake in peripheral tissues. The catecholamine surge also results in increased glucose production in the liver and glycogenolysis. In addition, inflammatory cytokines such as tumor necrosis factor- α , interleukin (IL)-1, IL-6, and C-reactive protein (CRP) induce peripheral insulin resistance.⁵ Up to 60% of patients in the pediatric intensive care unit (PICU) will have at least one blood glucose (BG) value higher than 150 mg/dL (8.3 mmol/L).⁴ Critical illness hyperglycemia, or stress hyperglycemia, has been associated with worse outcomes including higher risk of organ failure, longer stays in the intensive care unit (ICU), and higher mortality.^{1,4,7–9}

Tight Glycemic Control in Critically Ill Children

The association of hyperglycemia with increased morbidity and mortality has led practitioners and researchers to explore whether tight glycemic control (TGC) with intensive insulin therapy (ITT) administered intravenously would decrease these risks. However, the initial studies in critically ill adults have shown conflicting results. Researchers initially demonstrated a significant reduction in mortality and morbidity when TGC was undertaken.^{10,11} However, subsequent trials have been unable to reproduce these findings. In 2009, the Normoglycemia in Intensive Care Evaluation—Survival Using Glucose Algorithm Regulation (NICE-SUGAR) Study Investigators published a multicenter randomized controlled trial (RCT) of 6,104 adult patients who found that TGC (81–108 mg/dL [4.5–6 mmol/L]) increased the risk of mortality over conventional treatment (< 180 mg/dL [10 mmol/L]) (odds ratio [OR] for death in the intensive control group 1.14; $p = 0.02$), and increased the risk of hypoglycemia (6.8 vs. 0.5% in the intensive control and conventional groups, respectively;

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$p < 0.0001$), without a difference in treatment effect between surgical and nonsurgical patients. TGC did not produce benefit in terms of mortality, ICU or hospital length of stay, duration of mechanical ventilation, or need for renal replacement therapy.¹² These contradictory findings have resulted in glucose target recommendations in critically ill adults ranging anywhere from 140 to 180 mg/dL (7.8–10 mmol/L) and an inconsistent approach to their treatment.¹³

Pediatric Randomized Controlled Trials

Pediatric TGC studies have also produced inconsistent results, leading to many unanswered questions. This review will highlight the design and outcomes of the pediatric RCTs of TGC and discuss the known risks and benefits in particular subpopulations. A summary of the study designs and outcomes is provided in ► **Tables 1** and **2**, respectively.

The first study led by Vlasselaers et al¹¹ focused primarily on children postcardiac surgery with 45% of included children younger than 1 year. Almost all patients (99%) in the intensive insulin group received insulin compared with 46% of the patients in the conventional treatment group. The intensive insulin group achieved a mean of all BG concentrations of 94 mg/dL (5.2 mmol/L) in infants and 113 mg/dL (6.3 mmol/L) in children, whereas the conventional treatment group had means of 128 mg/dL (7.1 mmol/L) and 158 mg/dL (8.8 mmol/L) in infants and children, respectively (all $p < 0.001$). The intervention resulted in an attenuated inflammatory response, with a median change in CRP from baseline to day 5 of -6 (-28 to 15) mg/L in the intensive insulin group versus 0 (-12 to 29) in the conventional group ($p = 0.007$). It also resulted in reduced pulmonary and bloodstream infections, the rates of which (19.5 vs. 25.6% and 5.8 vs. 7.4% for the intensive insulin and conventional insulin groups, respectively) were markedly higher than comparable trials, likely attributable to the relatively liberal definition: “any suspected or documented secondary infection that was diagnosed after PICU admission by the attending senior intensive care physician and treated with systemic antimicrobials for more than 48 hours.”¹¹ TGC also resulted in reduced need for hemodynamic support, lower indicators of myocardial damage, shorter duration of ICU stay (► **Table 2**), and lower mortality risk (by 3.1%) from neurological or pulmonary complications in the intensive insulin group. The durations of mechanical ventilation, kidney dysfunction, and liver dysfunction were not affected.¹¹ The patients on the conventional insulin group had a higher mortality risk with an OR of 0.28 (0.09–0.79) corrected for baseline risk factors.

In this study, the risk of severe hypoglycemia < 40 mg/dL (2.2 mmol/L) was significantly higher in the intensive insulin group with one quarter of the patients having at least one episode and 5% having more than two episodes versus 1% ($p < 0.0001$) and none in the conventional group, respectively. Of the patients in the intensive insulin group who developed hypoglycemia, 80% were infants. Hypoglycemia was associated with a higher risk of death in this cohort, but the

finding was not statistically significant and was explained by the duration of ICU stay.¹¹

This group also performed a subgroup analysis of 14 neonates with transposition of the great arteries or truncus arteriosus, scheduled for surgery, who were assigned randomly to conventional insulin therapy or TGC (using a hyperinsulinemic-euglycemic clamp targeted at BG 50 to 80 mg/dL [2.8–4.4 mmol/L]) to evaluate the effect on cardiac function.¹⁴ By using this target BG range, they were able to demonstrate an attenuated inflammatory response and a decrease in markers of myocardial damage with TGC.¹⁴

A subsequent RCT by Jeschke et al studied glycemic control in burn patients. Despite randomization, patients in the intensive insulin-treated group were older and had a larger body surface area of third-degree burns compared with controls. Nonetheless, the incidence of infections and sepsis was reduced in the intensive treatment group to 8.2 versus 22.6% in the control group ($p < 0.05$). The patients in the intervention arm maintained an average BG significantly lower than the controls but did not consistently achieve BGs lower than 110 mg/dL (6.1 mmol/L) as expected by the study design. Average morning glucose levels in the intensive care arm were 120 to 130 mg/dL (6.7–7.2 mmol/L) and 150 to 160 mg/dL (8.3–8.9 mmol/L) in the controls. Intensive insulin treatment resulted in improved insulin sensitivity, improved bone mineral density, body fat, lean body mass, and body mass during admission. The resting energy expenditure did not differ between groups. The intensive insulin treatment group had a beneficial effect on fat metabolism, less risk of hepatomegaly, and improved serum markers of liver and kidney function.¹⁵ As in the study by Vlasselaers et al, intensive insulin treatment resulted in decreased inflammatory markers as compared with controls.

In contrast to the Leuven group,¹⁴ however, there was no effect on cardiac function, although the patients in the study by Jeschke et al did not have baseline cardiac disease. In the intensive insulin-treated group, 26% of patients had severe hypoglycemia compared with 9% in the control group ($p < 0.05$). Some of this risk is attributed by the authors to the care particular to burn patients including weekly operations and daily dressing changes, resulting in frequent interruption of their enteral feedings. The authors therefore suggest that for severely burned patients, a target BG of 130 mg/dL (7.2 mmol/L) might be more appropriate. The study was not powered to detect a difference in mortality.¹⁵

Next, a study by Agus et al (safe pediatric euglycemia after cardiac surgery [SPECs] trial) focused on a large group of children admitted to the cardiac ICU after cardiac surgery requiring cardiopulmonary bypass. Ninety-seven percent of the included children had at least one glucose measurement above 110 mg/dL (6.1 mmol/L). Most of the children (91%) in the glycemic control group received insulin compared with only 2% of the children in the standard care group ($p < 0.001$). Time-weighted glucose averages were 112 mg/dL (6.2 mmol/L) in the TGC arm and 121 mg/dL (6.7 mmol/L) in the standard care arm. Both the intention-to-treat analysis and the per-protocol analysis failed to show a difference between groups in the rate of health care–associated infections at 30 days after

Table 1 Randomized controlled trials of tight glycemic control in the pediatric ICU. Study design of included trials

Study	Location	Population	Sample size	Number of centers	Intervention	Insulin-dosing protocol	Hypoglycemia ^a	Primary outcome (s)
Vlasselaers et al (2009)	Belgium	Newborn to age 16 admitted to PICU for > 24 h	700	1	Control group: Insulin infusion for BG > 214 mg/dL and stopped if BG < 180 mg/dL (10.0 mol/L) Intensive group: 50–80 mg/dL (2.8–4.4 mmol/L) for infants 0–1 y; 70–100 mg/dL (3.9–5.5 mmol/L) for children 1–16 y	Dose adjusted by nurse	25% in the TGC group	CRP level and ICU length of stay
Jeschke et al (2010)	United States	Newborn to age 18 with > 30% body surface area burns requiring at least one surgery	239	1	Control group: target BG of 140–180 mg/dL Intensive group: target BG 80–110 mg/dL	Sliding scale to titrate insulin to goal BG	26% in the TGC group	Incidence of infection and sepsis, inflammatory response, hepatic and renal function
Agus et al (2012)	United States	Newborn to 36 mo postcardiac surgery	980	2	Control group: no set BG target range, patients were treated according to the preference of the attending cardiac intensivist (permissive hyperglycemia) Intensive group: BG target 80–110 mg/dL	Computerized insulin-dosing algorithm spreadsheet	3% in the TGC group	Number of health care-associated infections per 1,000 patient-d in ICU
Macrae et al (2014)	England	Newborn to age 16 expected to require mechanical ventilation and vasoactive drugs	1,369	13	Conventional glycemic control group: target BG of 180–216 mg/dL Intensive group: target BG 72–126 mg/dL	Treatment algorithm developed for the study	7.3% in the TGC group	Number of days alive and free from mechanical ventilation at 30 d

Abbreviations: BG, blood glucose; CRP, C-reactive protein; d, days; ICU, intensive care unit; PICU, pediatric intensive care unit; TGC, tight glycemic control.

^aHypoglycemia was defined as a blood glucose value < 40 mg/dL by all studies except Macrae et al in which it was defined as < 36 mg/dL.

Table 2 Randomized controlled trials of tight glycemic control in the pediatric ICU. Blood glucose ranges achieved and primary outcomes of included studies

Study	BG achieved by group		Primary outcome(s)					
	Control	TGC	p-Value	Outcome	Control	TGC	p-Value	
Vlasselaers et al (2009)	128 mg/dL (7.1 mmol/L) in infants ^a 158 mg/dL (8.8 mmol/L) in children ^a	94 mg/dL (5.2 mmol/L) in infants ^a 113 mg/dL (6.3 mmol/L) in children ^a	< 0.001	CRP change from baseline to d 5 (mg/L), Median	0 (– 12 to 29)	– 6 (– 28 to 15)	0.007	
Jeschke et al (2010)	150– 160 mg/dL ^b	120–130 mg/dL ^b	< 0.05	ICU length of stay, median	3 (2–7)	3 (2–6)	0.017	
				Incidence of sepsis, %	22.6	8.2	< 0.05	
				Acute phase response	CRP, IL-6, complement C3, α ₂ -macroglobulin, and haptoglobin, all significantly reduced in the intensive insulin group			< 0.05
				Hepatic and renal function	Decreased serum alkaline phosphatase, total bilirubin, creatinine, and postburn hepatomegaly in intensive insulin group			< 0.05
Agus et al (2012)	121 mg/dL (109–136) ^c	112 mg/dL (104–120) ^c	< 0.001	30-d rate of health care-associated infections—no. of infections/1,000 patient-d in the cardiac ICU	9.9	8.6	0.67	
Macrae et al (2014)	114.4 mg/dL ^d	106.8 mg/dL ^d	< 0.001	Number of days alive and free from mechanical ventilation at 30 d	23.6 ± 0.3	23.2 ± 0.3	Mean difference 0.36 (95% CI: – 0.42 to 1.14)	

Abbreviations: BG, blood glucose; CRP, C-reactive protein; d, days; ICU, intensive care unit; IL, interleukin; PICU, pediatric intensive care unit; TGC, tight glycemic control.

^aMean of all BG concentration.^bDaily 6:00 AM BG concentration.^cTime-weighted BG average (interquartile range).^dMean BG for all days.

randomization (►Table 2). TGC did not result in benefit with regard to mortality, length of stay, duration of mechanical ventilation, duration of vasoactive support, or other measures of organ failure.¹⁶

This study achieved the lowest rate of hypoglycemia among the TGC pediatric trials which the authors attribute to both the added monitoring of continuous glucose monitoring (CGM) systems, an explicit insulin-dosing algorithm and use of a blood-sampling device to minimize measurement errors. In addition, observed hypoglycemia was not associated with seizures, hemodynamic instability, arrhythmia, or any other identifiable symptoms.¹⁶

A post hoc subgroup analysis categorizing children as younger or older than 60 days of age suggested a benefit of TGC in lowering the risk of infection in children older than 60 days (OR for 30 days rate of health care–associated infections 0.39 [95% confidence interval [CI]: 0.15–0.92]). In contrast, patients younger than 60 days of age had a higher risk of health care–associated infections with TGC compared with standard care (OR: 3.68 [95% CI: 1.19–15.11]).¹⁷ We speculate that the difference in treatment effect might be associated to a more susceptible immune system in the older patients after maternally acquired, antibody-mediated immunity has waned, in addition to the higher susceptibility to protocol-associated hypoglycemia and anemia in the younger child. These results should be considered hypothesis generating rather than confirmatory but should prompt evaluation of the effects of TGC in infants versus older children in recent and future trials.

In the final study to date, Macrae et al studied 1,369 critically ill children who were expected to require mechanical ventilation and vasoactive drugs for at least 12 hours. The investigators estimated that to have 80% power to detect a difference of 2 days free of mechanical ventilation would require 1,500 patients; however, funding terminated before this goal was reached. Similar to the adult NICE-SUGAR trial, approximately one-third of subjects enrolled in the trial did not develop hyperglycemia. The number of days alive and free from mechanical ventilation was similar between the two groups, with a mean between group difference of 0.36 days (95% CI: –0.42 to 1.14) (►Table 2). There was no benefit to the particular subgroups that had been analyzed in previous studies (i.e., those who had cardiac surgery and those younger than 1 year of age), and no interaction with severity of illness scores (risk adjustment for congenital heart surgery [RACHS]-1 or pediatric index of mortality [PIM] 2 score). The investigators did find a lower requirement for renal replacement therapy (OR: 0.63; 95% CI: 0.45–0.89), but all other secondary outcomes did not show benefit for the TGC group, including length of stay, mortality, duration of mechanical ventilation or hemodynamic support, rate of infection, use of antibiotics, transfusions, pediatric logistic organ dysfunction (PELOD) score, rate of readmission, and costs.¹⁸

The rate of moderate hypoglycemia (defined as BG 36–45 mg/dL [2–2.5 mmol/L]) was 12.5% in the TGC group compared with 3.1% for those conventionally treated ($p < 0.001$). Severe hypoglycemia less than 36 mg/dL (2 mmol/L) was also more frequent in the TGC group (7.3 vs. 1.5%; $p < 0.001$). This study

is unique in that it demonstrated a highly significant association between having at least one episode of hypoglycemia and mortality, which was noted in the patients who had undergone cardiac surgery but not in the nonsurgical subgroup.¹⁸

What the Evidence Has Taught Us

Our group conducted a meta-analysis of these trials with a total of 3,288 subjects and concluded that TGC did not result in a significant decrease in 30-day mortality (OR: 0.79; 95% CI: 0.55–1.15; $p = 0.22$; Q statistic = 2.99 with $p = 0.39$; $I^2 = 0$) but was associated with lower infection rates when using the relatively liberal Leuven definition (OR: 0.76; 95% CI: 0.59–0.99; $p = 0.04$; Q statistic = 3.37 with $p = 0.34$; $I^2 = 11$), with all patients considered as a single cohort.¹⁹ It is evident from all of the studies that the risk of severe hypoglycemia is higher during intensive insulin treatment (OR of hypoglycemia with TGC by meta-analysis: 6.14; 95% CI: 2.74–13.78; $p < 0.001$; Q statistic = 11.28 with $p = 0.01$; $I^2 = 73$),^{11,15,16,18,19} though continuous glucose monitoring and a computerized insulin-dosing protocol appear to substantially reduce this risk.^{16,20}

Variability in Blood Glucose Targets, Patient Populations, and Outcomes

Tight glucose control is a complex and dynamic process; therefore, the utility of retrospective studies, where patients are treated with different insulin-dosing protocols and targets, is limited. Even among the randomized controlled studies, there is much variability in population included, study design, BG targets, and primary outcomes used to define power, which makes it challenging for the practicing clinician to reach an actionable conclusion.

Similarly, the difference in study populations adds difficulty in generalizing the results. There is a higher proportion of cardiac surgery patients studied in three trials,^{11,16,18} and one of the trials exclusively studied burn victims.¹⁵ The chosen primary outcomes to calculate power and sample size are reflective of the morbidity in the population studied, and thus are variable between studies as well. The total number of hyperglycemic critically ill children studied across all RCTs who were not burn patients, nor cardiac surgical patients, is approximately 347, not large enough to provide adequate power to test for the same primary outcomes according to the designs of the studies under review.

The BG targets for ITT in the positive study by Vlasselaers et al¹¹ were lower than those undertaken by the other three groups.^{15,16,18} Nonetheless, this lower BG range that resulted in decreased morbidity and mortality also significantly increased the risk for hypoglycemia compared with subsequent trials.¹¹ Severe hypoglycemia potentially adds risk. Furthermore, the actual separation in BG averages between treatment groups achieved by the trials (►Table 2) is different and might largely explain why the results are not consistent.

Risks of Hypoglycemia in the Developing Brain

Both hyperglycemia and hypoglycemia have been associated with deleterious effects on brain development and future cognitive performance.^{21–24} This is one of the reasons why

the increased risk of hypoglycemia is the most significant barrier to TGC. The rate of hypoglycemia has been consistently higher in TGC groups in clinical trials largely because the BG targets and achieved glucose concentrations are lower than standard care. The high rate of hypoglycemia in about a quarter of patients in the TGC groups was only ameliorated in the SPECS trial where TGC was aided by a computerized insulin-dosing algorithm and continuous glucose monitoring.^{16,20}

Whether the benefit of TGC justifies the added risk of hypoglycemia has been also studied. The control of hyperglycaemia in paediatric intensive care (CHiP) study led by Macrae et al found an association of hypoglycemia with higher mortality in the subgroup of cardiac surgery patients that was not evident in the other trials.¹⁸ Pediatric practitioners are also highly concerned about the potential effect of hypoglycemia on the developing brain. Variable patterns of brain injury have been seen in association with symptomatic hypoglycemia in young children, going from diffuse white matter injury to basal ganglia/thalamic abnormalities and cortical lesions, where the extent of injury correlates with the degree of neurodevelopmental impairment.²⁴ To this end, Vlasselaers et al followed their patients for 4 years after the study intervention and found no differences in neurodevelopmental testing, including intelligence, visual-motor integration, or memory, between patients treated with TGC versus those in standard care.²⁵ In this study, TGC appeared to improve motor coordination and cognitive flexibility. The lack of harm was attributed to the reduction in glycemic variability and presumed brevity of periods of hypoglycemia, although no continuous glucose monitoring was performed.²⁵ This is supported by previous studies of hypoglycemic neonates where early transient hypoglycemia not associated with seizures resulted in normal or only mildly abnormal neurocognitive development in infancy, whereas infants who had prolonged or severe hypoglycemia had worse outcomes.²⁴ The neurodevelopmental follow-up data for the SPECS trial suggest that while there was no difference between treatment groups, there was a statistically significant decrement in Bayley Development score among those with moderate or severe hypoglycemia when compared with those with mild or no hypoglycemic events (composite Bayley-III [2006] scores for cognitive development: 95.0 ± 10.7 vs. 104.7 ± 11.5 ; $p = 0.02$, language 86.5 ± 16.5 vs. 97.7 ± 11.6 ; $p = 0.009$, and motor development 82.4 ± 14.4 vs. 92.8 ± 13.3 ; $p = 0.03$).²⁶

In conclusion, the risks of severe hypoglycemia in pediatric patients are not negligible. However, because standard treatment of hyperglycemia in the ICU also incurs risks, the benefits of TGC in critically ill pediatric patients can only be weighed against these if TGC can be conducted in a standardized manner that lowers the risk of hypoglycemia to a minimum; a goal that has been proven to be feasible. Furthermore, the variability in the results of well-designed RCTs proves that recommendations cannot be generalized to all critically ill pediatric patients who develop hyperglycemia and rather that we will have to develop condition-specific recommendations that will need to be informed by ongoing

studies that include a larger, more generalizable sample of hyperglycemic, noncardiac surgery, critically ill patients.

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