Journal of Diabetes Science and Technology
Volume 6, Issue 1, January 2012

SYMPOSIUM

Glycemic Control in the Pediatric Intensive Care Unit of Leuven: Two Years of Experience

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Abstract

Stress hyperglycemia and hypoglycemia are associated with increased mortality and morbidity in critically ill patients. Three randomized controlled trials, in the surgical, medical, and pediatric intensive care unit (PICU) of the Leuven University in Belgium, demonstrated the beneficial response of tightly controlling blood glucose levels within age-adjusted narrow limits by applying intensive insulin therapy. Follow-up studies could not confirm the results obtained in the Leuven studies but revealed the complexity associated with tight glycemic control (TGC). This article gives an overview of the methodological aspects typical of the Leuven TGC concept, with the focus on the PICU. Differences between the adult and the PICU are described. This overview article might help other ICUs by addressing potential differences in clinical practice when implementing TGC.

J Diabetes Sci Technol 2012;6(1):15-21

Introduction

Critically ill patients have a severe dysregulation of their glucose homeostasis. Observational studies have shown that both hyperglycemia and hypoglycemia are associated, by a J-curved relation, with increased mortality rate in patients with severe illness.[1] This association between stress hyperglycemia and poor outcome is known not only for critically ill adults but also for critically ill infants and children.[2–7] Normalization of blood glucose levels within age-adjusted tight limits (tight glycemic control, TGC) leads to a reduction in the mortality and morbidity rate as was shown in three randomized controlled trials in the surgical, medical, and pediatric intensive care unit (PICU) of the Leuven University in Belgium.[8–10] The trial in the Leuven PICU was performed with 700 infants and children who were randomly allocated to the intensive insulin therapy (IIT) group or the conventional insulin therapy (CIT) group.[10] The target blood glucose ranges in the IIT group were the age-adjusted normal fasting levels of glycemia: 50–80 mg/dl for infants and 70–100 mg/dl for children. In the CIT group, insulin was administered only to prevent blood glucose levels from exceeding 215 mg/dl (which is the renal threshold). An important reduction in the duration of PICU stay, inflammatory response, and mortality was noted.

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Abbreviations: (CIT) conventional insulin therapy, (ICU) intensive care unit, (IIT) intensive insulin therapy, (IU) insulin unit, (KCl) potassium chloride, (NaCl) sodium chloride, (PICU) pediatric intensive care unit, (TGC) tight glycemic control

Keywords: blood glucose, children, critically ill patients, infants, tight glycemic control

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Inevitably, IIT also led to an increased incidence of (short-lasting) hypoglycemia: approximately 25% patients had at least one hypoglycemic event (blood glucose < 40 mg/dl) during their entire stay in the PICU.

The fear of causing iatrogenic hypoglycemic episodes,[11] in addition to some follow-up clinical trials that either could not confirm this survival benefit or have even resulted in an increased mortality in patients who were treated with IIT,[12–14] have led to controversies on IIT and TGC. First of all, in many PICUs worldwide, the fear of hypoglycemia outweighs the fear of hyperglycemia.[11,15] However, the causality between iatrogenic short-lasting hypoglycemia and ICU mortality is not clear. Rather, it has been suggested that brief hypoglycemic events may be an indicator of severe illness. Patients with spontaneous hypoglycemia, which is a typical result of liver and/or kidney failure, have a higher risk of dying.[16,17] A long-term follow-up study examining the impact of both hypoglycemic and hyperglycemic episodes on neurocognitive development in infants and children who participated in the Leuven PICU study is currently ongoing (*http://www.clinicaltrials.gov*, identifier NCT00214916) and will further clarify this hypoglycemia issue. Second, the follow-up clinical trials with critically ill adult patients that did not confirm the results obtained in the Leuven studies suffered from different methodological issues as was already extensively explained by Van den Berghe and colleagues.[18,19] Currently, the ICU community agrees that the methodological aspects of TGC have been underestimated, possibly resulting in larger than expected swings in blood glucose levels. A multicenter, prospective randomized controlled trial comparing two glycemic targets in critically ill children and infants, called the Control of Hyperglycemia in Pediatric Intensive Care trial (ISRCTN61735247), is currently ongoing.[20]

This article gives an overview of the methodological aspects typical of TGC and IIT with critically ill children/infants that are currently considered in clinical practice in our hospital. Although many general aspects are also valid for the Leuven adult ICU, this article focuses on the Leuven PICU.

Start of Tight Glycemic Control

Admission of a critically ill patient to the ICU is synonymous with starting the control of blood glucose levels. More than 90% of these patients are mechanically ventilated, explaining the need to take a blood gas as soon as the patient arrives. This first blood gas is typically used to tune the ventilation machine and delivers the first blood glucose value. Because the glucoregulatory system behavior of the new patient is not known at admission, a rudimentary insulin infusion scheme is utilized to determine the starting insulin dose:

- Children (>1 year)
  - If blood glucose >200 mg/dl, 0.2 insulin unit (IU) per kg body weight per hour is given,
  - If blood glucose >100 mg/dl, 0.1 IU per kg body weight per hour is given,
  - Else, insulin is not administered.
- Infants (0–1 year)
  - If blood glucose >160 mg/dl, 0.2 IU per kg body weight per hour is given
  - If blood glucose >80 mg/dl, 0.1 IU per kg body weight per hour is given
  - Else, insulin is not administered.

Further, insulin infusion concentrations depend on the body weight of the patient. As a rule of thumb, the following infusions are prepared:

- Body weight <15 kg: 10 IU per 50 ml of 0.9% sodium chloride,
- 15 kg ≤ body weight ≤ 30 kg: 20 IU per 50 ml of 0.9% sodium chloride,
- Body weight >30 kg: 50 IU per 50 ml of 0.9% sodium chloride.

Blood Glucose Sampling

Only when an arterial line is *in situ* will TGC be done, as frequent blood glucose measurements are essential. The ABL700 analyzer (Radiometer Medical A/S, Copenhagen, Denmark) is used in our PICU to measure the blood glucose concentration in undiluted arterial blood. The system corrects the obtained values toward plasma glucose concentrations, is accurate in a critically ill setting, and generates a reliable result in a short time period.[21,22] The advantage of using a blood gas analyzer is the simultaneous measurement of a set of parameters (e.g., potassium, oxygen, lactate, hemoglobin, etc.) rather than taking a blood sample just for glucose value measurement.

Indeed, many parameters have to be measured frequently (e.g., 4 h time interval) in an ICU environment for other reasons than blood glucose control (e.g., adjustments of mechanical ventilation settings). Then, the simultaneous measurement of the glucose level does not lead to an increased workload for the nurses (current nurse/patient ratio in Leuven is 1:2).

Furthermore, it is important to select a measurement methodology that has been clinically validated in a critically ill setting (accuracy and reliability[23]) and that is user-friendly (easy to use and results are available immediately). Many point-of-care glucose meters that are widely used in the treatment of patients with diabetes and that generate a result within a short period of time are unfortunately not adequate sensor devices for use in the specific setting of the critically ill. Acidosis, high partial pressure of oxygen levels, anemia, and several drugs are typical disturbance factors that preclude accurate glucose measurements.[21,24,25] The resulting measurement errors may even go in the opposite directions for the hypoglycemic and the hyperglycemic range, which makes the targeting of a narrow glucose range even more complicated.

Next, glucose measurements should be based on arterial blood samples. In our PICU, only in exceptional cases, venous blood is sampled for glucose measurements. Obviously, strict procedures must be followed to avoid misinterpretations when using one multiple lumen catheter for both sampling venous blood and administering glucose nutrition and/or medication (e.g., aspiration of a mix of venous blood and glucose nutrition may lead to overestimation of the blood glucose and wrong clinical decisions with respect to the insulin dose). Capillary sampling should be avoided when applying TGC in an ICU setting because of inaccurate measurements.[26,27]

Sampling Frequency

Blood glucose is sampled every hour in the initial phase after admission. Once the glucose signal is stable and enters the normoglycemic target range, the sampling interval is gradually increased to 4 h. Four hours is also the maximum sampling interval. Some circumstances, as listed below, require a shorter sampling interval (e.g., 1 h):

- Steep rise of blood glucose,
- Steep fall of blood glucose,
- Temporary nutrition stop or other important adjustments of the nutrition flow,
- Important adjustments of insulin dosage, and
- Severe hypoglycemia (blood glucose < 40 mg/dl).

When needed, a control blood glucose is sampled 30 min after the previous measurement (e.g., in case of severe hypoglycemia, steep fall of blood glucose that may lead to severe hypoglycemia). Because general blood gas sampling is also required for parameters other than the blood glucose (as discussed earlier), the number of blood samples specifically required for controlling glucose levels are acceptable.

Insulin Infusion

In the Leuven PICU, insulin is always administered to the patient by means of a syringe-driven infusion pump that continuously delivers insulin through a central venous catheter (central line). The insulin concentration depends on the body weight of the infant/child (see aforementioned text). The continuous infusion of insulin facilitates the control of blood glucose as bolus administrations potentially increase blood glucose variability. The use of syringe-driven infusion pumps outperforms the use of volumetric pumps, which may deliver various amounts of insulin over time. Insulin also has an absorptive nature towards the surface of its package material.[28] This surface binding can lead to inadequate insulin delivery (overestimation of the insulin concentration) and, subsequently, to inefficient blood glucose control. The use of hard plastic package material, the daily replacement of the insulin infusion solution (every 24 h or sooner in case of insufficient supply), and the implementation of syringe-driven infusion pumps provide a stable insulin delivery.

Control of Blood Glucose

After the initial phase (see aforementioned text), the insulin dose is adequately adjusted by 0.01–1 IU/h. Although a rudimentary insulin infusion *guideline* exists,[10] the bedside nurses control the blood glucose levels particularly based on their intuition and experience. This "intuition" is founded on the evolution of blood glucose, insulin, and nutrition. Next, the nurses anticipate the varying insulin resistance when changes are caused by external factors. Increased insulin resistance (and the corresponding increased insulin need) is associated with administration of glucocorticoid, increased body temperature (symptom of

infection), or physical stress (e.g., weaning from mechanical ventilation). Important to note is that changing insulin resistance is not always predictable (due to varying internal factors). The insulin sensitivity increases (or the insulin resistance decreases) typically with patients who are recovering from their illness, even if all potentially influencing external parameters remain stable.

Moreover, both the nutrition load and the insulin infusion are stopped for any transportation of the patient (e.g., to the operating room, the scan room). The insulin flow is further reduced proportionate to the reduction of caloric intake or even temporarily stopped when feeding is interrupted. When the PICU-patient starts eating, the critical phase has passed. Intensive insulin therapy is stopped when the majority of the caloric intake is realized by oral intake. Only for patients with a known background of diabetes mellitus, glucose control will be continued based on their insulin infusion regimen that they were used to before their admission to the PICU.

In summary, the insulin infusion guideline has to be applied with common sense by taking into account influencing parameters such as caloric intake, actual and previous blood glucose levels, previous insulin dosages, and patient's sensitivity to insulin. The derivative of these parameters (i.e., steepness of changes) plays a major role. It is clear that the list of guidelines applicable in our PICU is merely a *guide* and should not be implemented literally. However, intuitive anticipating decision-making is a *must* when aiming at the age-adjusted normoglycemic target ranges while avoiding glycemic fluctuations (alternating hypoglycemic and hyperglycemic episodes).

Hypoglycemia

A crucial element in the control of blood glucose levels is the avoidance of hypoglycemic events. Because normoglycemic target ranges in critically ill children and infants lie close to the hypoglycemic alarm level,[29] a higher incidence of (short-lasting) hypoglycemia is typical of IIT. Brief hypoglycemic episodes were also observed in the PICU randomized controlled trial.[10] During the entire stay at the ICU, at least one blood glucose level ≤ 40 mg/dl was monitored in 25% of the patients treated by IIT. Despite this high number of hypoglycemic events, the mortality degree was lower in the IIT group than in the conventionally treated patient group.

In the event of hypoglycemia, a fast return to normoglycemia without evoking hyperglycemia is important to avoid glycemic fluctuations. Low blood glucose levels should not be overcompensated within a short time, as this may be worse than the actual hypoglycemic event.[16,17,30] It has even been suggested that blood glucose fluctuations may be worse than tolerating moderately hyperglycemic levels. Additional *control* blood glucose measurements can be necessary in case of severe hypoglycemia (e.g., 30 min time interval).

In our PICU, hypoglycemia is treated as follows. Insulin infusions are heavily tapered when reaching the lower limit of the target (50 mg/dl for infants and 70 mg/dl for children) and immediately stopped when blood glucose values are below 40 mg/dl for infants and 50 mg/dl for children. Additionally, a glucose bolus (1 ml/kg of 50% dextrose solution) is administered when glycemia levels are lower than 30 mg/dl for infants and 40 mg/dl for children. These instant glucose intakes can be repeated when blood glucose levels remain low. Additional follow-up blood gas sampling within a short time interval is a crucial factor in the recovery of a hypoglycemic event.

Control of Potassium

The final component of the Leuven IIT protocol is the control of the potassium level. A side effect of insulin therapy is the resulting shift of potassium from extracellular to intracellular compartment. However, this natural behavior may further induce hypokalemia and subsequently arrhythmias. As each blood glucose measurement is based on an arterial blood sample using an accurate point-of-care blood gas analyzer, other parameters (such as the potassium level) are also simultaneously determined (see aforementioned text). Potassium levels have to be measured at least every 4 h. Low potassium levels (<3.5 mmol/liter) are corrected by intravenous delivery of potassium to restore normal kalemia (4–4.5 mmol/liter). The amount of intravenous potassium supplement for critically ill children/infants without renal insufficiency is pragmatically computed as follows:

$$A = \frac{\text{Body weight (kg)}}{3},$$

where A is the amount of potassium chloride per hour (expressed as mEq KCl/h), aiming at 1 mmol/liter increase of the potassium level.[31] The maximum amount of potassium chloride per hour is set at 4 mEq KCl/h. Using this methodology, episodes of hypokalemia and hypokalemia-induced arrhythmia can be avoided.[19] In addition, we want to point out that, besides controlling blood glucose levels, the control of potassium levels is also autonomously performed by the bedside nurses in

our (P)ICU. Finally, the use of bolus insulin injections, volumetric insulin pumps, and handheld glucometers (that cannot be used to measure potassium and, therefore, cannot detect potential hypokalemia) enhances the risk of hypokalemia and should be avoided accordingly.

Differences between Adults and Children/Infants

Though the main principles are similar to the adult ICU, the following list gives a brief overview of the most important differences between the methodology of TGC and IIT in the treatment of critically ill adult patients and critically ill children/infants.

- The (age-adjusted) blood glucose target range is lower in the PICU. The normoglycemic range is set at 50–80 mg/dl for infants and 70–100 mg/dl for children, whereas the target range for adults is 80–110 mg/dl. These lower glycemic goals may provoke potentially severe hypoglycemia (<40 mg/dl) more easily, which explains the extra attention required when implementing TGC in the PICU.

- The insulin sensitivity of critically ill children/infants is much higher compared with the adult population. Sometimes, virtually marginal adaptations of the insulin infusion rate (e.g., 0.01 IU/h) are necessary to adequately control the blood glucose within the aforementioned narrow target limits in the PICU. The minimum insulin flow change in the adult ICU is typically higher (0.2–0.5 IU/h).

- The insulin concentration in the PICU is dependent on the body weight of the child/infant (see aforementioned text) to restrict fluid infusion. Insulin concentrations for the critically ill adult population are mostly 50 IU per 50 ml of 0.9% sodium chloride (NaCl). For adult patients with high insulin needs or high fluid input, the insulin concentration is doubled: 100 IU per 50 ml of 0.9% NaCl.

- Potassium control: the calculation of the amount of intravenous potassium supplement for critically ill adults without renal insufficiency differs from the children/infants formula. In case of the critically ill adult population,

$$A = \frac{\text{Body weight (kg)}}{2},$$

with A representing the amount of potassium chloride per hour, administered intravenously, for 1 mmol/liter rise of the potassium level (with a maximum of 20 mEq KCl/h).[31]

- Transition protocol: the procedure for ICU-discharge to the general ward is a final methodological difference (with respect to TGC). When patient discharge is announced and with insulin infusions lower than 2 IU/h, insulin infusion is stopped in the adult ICU. Next, the blood glucose level is measured at time instant of actual discharge. In case of glucose values higher than 180 mg/dl, glycemia is followed-up at the general ward. With insulin infusions higher than 2 IU/h, the diabetologist from the receiving unit is contacted. However, in the PICU, children or infants are *never* discharged to the general ward with an insulin infusion line. Nurse-driven exogenous insulin is stopped at least 2 h before actual discharge. At time instant of actual discharge, a final blood glucose is measured. Patients with formerly known diabetes control their glucose levels based on their proper insulin infusion regimen. The diabetologist from the receiving unit is also contacted.

Conclusion

Stress hyperglycemia during critical illness is strongly associated with poor outcomes. Targeting blood glucose levels towards narrow age-adjusted limits demonstrated an improvement of short-term outcome of patients admitted to the Leuven adult ICU and the Leuven PICU. However, implementation of TGC in other ICUs indicates the complexity of the methodology used. This article has described the methodological aspects typical of TGC and IIT in critically ill children/infants who are in the current clinical practice in the Leuven PICU. Potential issues from admission to discharge when applying TGC have been discussed in sequence: starting TGC-protocol immediately after admission, blood gas sampling (and sampling frequency), insulin infusion, factors that influence blood glucose control, treatment of hypoglycemic events, and control of potassium levels. Finally, we want to stress that the passion and dedication of the nursing staff are prerequisites of efficient and well-performed implementation of IIT. Nurses have been given the responsibility to apply the *full* IIT concept. Succeeding in adequately normalizing glycemic levels makes them proud and honored.

Funding:

This research is supported by Flemish Government, FWO: G.0557.08 (for Tom Van Herpe, Bart De Moor, Greet Van den Berghe); Industrial Research Fund (IOF): HB/10/039 and IWT: TBM project 100793 (for Tom Van Herpe, Dieter Mesotten, Bart De Moor, Greet Van den Berghe); postdoctoral fellowship of the Clinical Research Fund, University Hospitals Leuven (for Dieter Mesotten); Research Council KUL: GOA/11/05 AMBioRICS, GOA/10/09 MaNet, CoE EF/05/006 and PFV/10/002, IOFSCORES4CHEM, several Ph.D./postdoc, and fellow grants; Flemish Government, FWO: Ph.D./postdoc grants, projects G0226.06, G0321.06, G.0302.07, G.0320.08, G.0558.08, G.0588.09; research communities; G.0377.09; IWT: Ph.D. grants, Eureka-Flite+, SBO LeCoPro, SBO Climaqs, SBO POM, O&O-Dsquare; Belgian Federal Science Policy Office: IUAP P6/04; IBBT; EU: ERNSI; FP7-HD-MPC (INFSO-ICT-223854), COST intelliCIS, FP7-EMBOCON (ICT-248940), FP7-SADCO (MC ITN-264735), ERC HIGHWIND (259 166); Contract Research: AMINAL; Helmholtz: viCERP; and ACCM (for Bart De Moor); and Research Council KUL: GOA/2007/14; Flemish Government, FWO: G.0533.06; and Methusalem Programme funded by the Flemish Government (for Greet Van den Berghe).

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