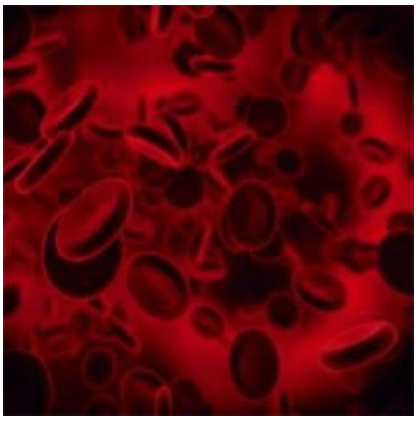
ICU
MANAGEMENT & PRACTICE

ICU Volume 11 - Issue 1 - Spring 2011 - Series

How Should We Control Blood Glucose in 2011?



Dr. Jean-Charles Preiser, MD, PhD
******@***erasme.ulb.ac.be

Department of Intensive Care,
Erasme University Hospital
Brussels, Belgium

Prof. Jean-Louis Vincent, MD, PhD
Editor-in-Chief, ICU Management & Practice
******@***icu-management.org

Professor - Department of Intensive Care Erasme Hospital
Université libre de Bruxelles
Brussels, Belgium

LinkedIn Twitter

Many studies, some already published a long time ago, have reported that hyperglycaemia (Dungan et al. 2009), or "dysglycaemia" (Smith et al. 2010) as some prefer, is an independent prognostic marker in acutely ill patients. For example, after cardiac surgery, glycaemia above 180 mg/dl, implying poor glucose control, was consistently and independently associated with an increased rate of postoperative infections and mortality (Furnary et al. 2003). The beneficial effects of lowering blood glucose to less than 150 mg/dl are well recognised and have been reported by retrospective analyses of large cohorts of critically ill patients (Falciglia et al. 2009).

The landmark Leuven I trial was a prospective, randomised controlled study that showed that "tight" glucose control (target blood glucose 80-110 mg/dl) improved survival and several secondary outcome variables (incidence of systemic infection, acute renal failure, need for transfusions polyneuropathy, duration of mechanical ventilation and length of stay in the intensive care unit [ICU])

(van den Berghe et al. 2001). However, seven independent confirmatory studies failed to reproduce these results (Annane et al. 2010; Arabi et al. 2008; Brunkhorst et al. 2008; De La Rosa et al. 2008; Finfer et al. 2009; Preiser et al. 2009; van den Berghe et al. 2006a). In the largest study, the NICE-Sugar study, there was even a worse outcome associated with tight glucose control (Finfer et al. 2009). Because of the lack of external validity of the findings of the Leuven I trial, recent evidence-based guidelines no longer recommend a tight target for blood glucose in critically ill patients (Ichai et al. 2010; Moghissi et al. 2009). Expert opinion and actual clinical practice commonly use an intermediate threshold to start insulin therapy, most often 140-150 mg/dl (Krinsley et al. 2008; Vincent, 2010). The feasibility and safety of tighter glucose control cannot be guaranteed unless considerable technological improvements become available.

The implementation of tight glucose control is a complex process, involving a number of important factors (Schultz et al. 2010). Each step of glucose control is critical, from the blood sampling, through choice of analyserand algorithm, to administration of the correct amount of insulin. Importantly, errors in insulin administration are the commonest therapeutic mistakes in the ICU (Garrouste-Orgeas et al. 2010). Moreover, certain physiologicalquestions related to glucose control in critically ill patients remain unanswered, but suggest that the 'optimal' blood glucose target is still undefined. Indeed, rather than being a fixed target for all patients, it is likely that the 'ideal' blood glucose concentration varies in individual patients. Based on these uncertainties and unresolvedissues, what changes and progress can we expect in the near future? How can we move forward?

Better Delineation of the Risks Associated with Tight Glucose Control

The price to pay for tight glucose control includes an increased risk of hypoglycaemia and additional workload for the nursing staff. The incidence of hypoglycaemia, defined as the percentage of patients who experienced at least one episode of blood glucose of < 40 mg/dl, increased by a mean factor of 6 in patients randomised to tight glucose control with in- tensive insulin therapy (Lacherade et al. 2009; Preiser et al. 2010). The mortality rate of the patients with hypoglycaemia was multiplied by a factor of 2.5 (Preiser 2009). Two independent sets of data (Egi et al. 2010)(Krinsley et al. Unpublished data) suggest that the occurrence of even mild hypoglycaemia (< 80 mg/dl) is associated with increased mortality rates. Recently, Duning et al reported subtle neurocognitive dysfunction in patients who experienced hypoglycaemia during their ICU stay (Duning et al. 2010). The thresholdused to define hypoglycaemia may, therefore, be different in ICU patients compared to the non-critically ill. In any case, avoidance of hypoglycaemia represents a key challenge during glucose control in the ICU. Likewise, high degrees of glucose variability, which are associated with poorer outcomes (Ali et al. 2008; Egi et al. 2006), are closely related to hypoglycaemia and its correction. Indeed, in vitro, large changes in glucose concentration of theculture medium of human cells is associated with cellular damage and increased oxidative stress and apoptosis (Risso et al. 2001). Hence, achievement of minimal glucose variability represents another major challenge of glucose control. A clinically relevant definition of glucose variability is also needed, as most of the many indices available have not been assessed in an ICU setting (Ali et al. 2009).

What is the Most Appropriate Glycaemic Target?

This key question is still unanswered. The most appropriate target is likely to be influenced by patient-related factors, such as the type and severity of critical illness and the medical history, and by ICU-related factors, e.g., staffing, available technology and local practice. Several lines of evidence support the absence of a universal 'optimal' blood glucose target in critically ill patients. In the ICU, the term 'normoglycaemia' is probably inappropriate for a blood glucose value between 80 and 110 mg/dl; these values are considered to rule out carbohydrate intolerance in fasting outpatients whereas critically ill patients undergo metabolic stress,are treated with medications that may increase blood glucose (catecholamines, steroids, etc) and are usually fed (Preiser 2008). Hyperglycaemia can also be viewed as a physiological consequence of the adaptive stress response (Dungan et al. 2009).

Additional physiological evidence supports different optimal blood glucose targets in specific situations. After brain injury, hypoglycaemia (< 80 mg/dl) and moderate hyperglycaemia (> 150 mg/dl) are both associated with poor outcome (Oddo et al. 2008; Vespa 2008). In patients with sepsis, no benefit was associated with the achievement of tight glycaemic control (Brunkhorst et al. 2008). In addition, in the Leuven cohorts (van den Berghe et al. 2006b) as well as in the patients of the Glucontrol and NICE-SUGAR studies (Finfer et al. 2009; Preiser et al. 2009), tight glucose control was not beneficial in the subsets of patients with pre-existing diabetes.

Conversely, after cardiac surgery (two thirds of the patients in the Leuven I study), there was a clear benefit with tight glucose control (van den Berghe et al. 2001). Of interest, surgical patients treated

with tight glucose control had a better outcome in surgical ICUs than surgical patients treated with tight glucose control in mixed ICUs (Friedrich et al. 2010). Taken together, these findings support different 'optimal' blood glucose concentrations according to patient- and ICU-related factors.

Blood Glucose Measurement

Wide variations exist in the techniques used to measure blood glucose, including sampling site and the device used. Although widely used in ICUs, the accuracy and reliability of commercially available point-ofcare (POC) devices are not sufficient, especially when capillary samples are used.

POC glucose readers use different measurement methods (amperometric or colorimetric reaction), enzymatic reactions (glucose oxidase or glucose dehydrogenase), calibration on total blood or on plasma, and different blood volumes, all of which lead to devicespecific limitations, interference, and technical constraints that need to be taken into ac count when interpreting a blood glucose value. The reliability of the results depends on the user's knowledge of the device. Improved accuracy of POC devices is definitely needed in the lower ranges of blood glucose values, especially when capillary samples are used (Kanji et al. 2005; Vlasselaers et al. 2008). The current official requirements and international norms are based on data and therapeutic requirements for diabetic, but not critically ill patients. For example, the Clarke error grid introduced in 1987 and used to evaluate the therapeutic implications of inaccuracies of glucose readers (Clarke et al. 1987) is not adapted for insulin algorithms currently used in ICUs. Improvements in POC technology need to include the introduction of correction factors or compensation for interference and sampling site. Assessments of performance also need to be carried out in an ICU environment.

Continuous glucose monitoring will probably represent a major step forward, initially for clinical research and later for clinical use. Some experience with subcutaneous continuous glucose monitoring has already been reported (Brunner et al. 2011; Corstjens et al. 2006), but the accuracy of these devices is currently too low in haemodynamically unstable patients. The major hope lies in continuous intravascular glucose monitoring. Limited clinical data, using various techniques (enzymatic, microdialysis, optic fibre), have been published (Rooyackers et al. 2010), but several companies are currently developing new prototypes, which will be evaluated in the near future (Fahy et al. 2008; Joseph et al. 2009; Mraovic 2009). The methods by which these continuous glucose sensors are evaluated will hopefully also be standardised.

Insulin Algorithms

A large number of insulin algorithms are used today (Wilson et al. 2007). Use or misuse of these algorithms can partially explain the discrepancies in the results from the large clinical trials on tight glucose control. Although there is consensus regarding the preferential use of dynamic scales, the comparison of algorithm performance if not standardised (Eslami et al. 2008). Computer-based algorithms can improve the quality of glucose control (Juneja et al. 2009), as long as individual patient characteristics are incorporated and taken into account in the calculation of the insulin infusion rate. For example, Lonergan et al. (2006) developed and validated a protocol which included the actual insulin sensitivity. Using this protocol, the quality of glucose control in the Glucontrol study (Preiser et al. 2009) would have been improved (Suhaimi et al. 2010).

Closed-Loop Systems

The ultimate innovation in the field could be the development of closed-loop systems that mimic an artificial pancreas. In such techniques, (near-) continuously measured blood glucose values can be fed into computerised

systems which then adapt the insulin infusion rate accordingly, taking into account specific patient- and treatment-related variables. Preliminary data with closedloop systems have already been published, and suggest that this approach may decrease variability in blood glucose concentrations (Yatabe et al. 2011) but further clinical studies are needed to determine whether this effect can influence outcomes.

Conclusion

Much has changed in our approach to blood glucose concentrations in critically ill patients over the last decade. The Leuven studies encouraged us to pay greater attention to maintaining blood glucose at levels much lower than had previously been considered necessary. But the risks of tight glucose control then became apparent along with realisation that variability in blood glucose

concentrations was also relevant to outcomes. The development of techniques to continuously monitor blood glucose levels will help follow blood glucose levels more closely and closed-loop systems by which insulin doses will be adjusted automatically according to continuous blood glucose readings and adapted to individual patient characteristics are just over the horizon. Until then, blood glucose levels below 150 mg/dl should be targeted and attempts made to limit variations in blood glucose levels as much as possible (Vincent 2010).

Published on : Thu, 15 Aug 2013