Blood sugar control in the intensive care unit: time to relook

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Abstract:
The choice of blood sugar control technique in the ICU has long been debated. Intensive insulin therapy to achieve normoglycaemia has been shown to reduce mortality, morbidity and the length of ICU stay; but, at the same time it also requires frequent glucose monitoring, adjustment of insulin dose and increase in the medical personnel workload. Despite its clinical benefits, intensive glucose control (IGC) is, however, not favoured by the intensivist, because of the risk of hypoglycaemia. This article provides the reader with an interesting thought: Can intensive blood sugar control be implemented in the ICU, while avoiding hypoglycaemia, and without an increase in hospital cost, and thus change existing blood sugar control protocols in the ICU? Is this possible with the use of continuous glucose monitoring (CGM) devices, which have recently emerged as a tool to maintain proper glucose levels? If further developed, CGM technology could ultimately prove clinically useful in the ICU. However, further research is warranted to confirm its benefits in the implementation of tight glucose control policies in the ICU.

Key words: blood glucose, continuous glucose monitoring, intensive care, intensive glucose control.

Introduction

The impact of glycaemic control on in-patient mortality has been long debated and the optimal target range for blood glucose in critically ill patients remains unclear. Hyperglycaemia, defined by a blood-glucose level exceeding the normal fasting level of 5.5 mmol/l is common during critical illness.1 Glucose elevation in critically ill patients is commonly attributed to associated increased levels of cortisol, glucagon and adrenaline, thus resulting in increased gluconeogenesis and decreased peripheral uptake of glucose, hence leading to high circulating levels of glucose.2 This glucose elevation increases the cellular glucose overload and associated pronounced side effects of glycolysis and oxidative phosphorylation, thereby causing irreversible damage to cellular function and structure, reflected by various organ dysfunctions (liver, renal, cardiac, endothelial and cellular immune system).3,4 Although this stress hyperglycaemia was long deemed to be a beneficial, adaptive response to provide energy to those organs that predominantly rely on glucose as metabolic substrate, many studies have confirmed that there is a link between hyperglycaemia and increased mortality.1 In fact, Mesotten D and Van den Berghe G,5 showed that the statistical association between blood-glucose level and risk of death, in many observational studies follows a J-shaped curve, with normal, fasting blood levels associated with lowest risk of death.

Intensive versus conventional glucose control

The choice of blood sugar control technique (conventional versus intensive control) in the ICU, however, has long been debated. Insulin-based treatment regimens decrease morbidity and mortality in critically ill patients,6 yet tight control of blood sugar, was not favoured by many intensivists – due to an increased risk of hypoglycaemia. Hypoglycaemia remains the most significant concern regarding implementation of tight glucose control policies because it can induce irreversible brain lesions. Severe hypoglycaemia (<2.2 mmol/l)7 has been shown to be an independent risk factor for mortality in the ICU8 and it occurs 5-10 times more in intensive glucose control (IGC) as compared to conventional glucose control (CGC). Moreover, as the majority of ICU patients have decreased levels of consciousness and increased stress, the detection of hypoglycaemia in these patients depends solely on glucose monitoring.

From an economic standpoint, a cost analysis study of IGC in critically ill adult patients revealed that IGC saved an average of $1580 per patient9 attributed to shorter ICU and hospital length of stay, decreased ventilator-dependent days, and reduced total laboratory costs. In another study on mechanically ventilated patients admitted to a surgical ICU, the excess cost of hospitalisation in patients treated with CGC compared to those treated according to the IGC regimen was €2638 per patient.10 Hence, given the improved clinical outcomes of IGC and its cost effectiveness, it is probably worth pursuing.

To show a relationship between hyperglycaemia and mortality risk, many randomised controlled trials (RCTs) that target and achieve different blood-glucose levels have been conducted. The 2001 Leuven Surgical Trial11 was one of the first to demonstrate a clinical benefit amongst predominantly surgical ICU patients treated with IGC. Subsequent RCTs were then conducted in a heterogeneous population in ICU, but these studies failed to support the subsequent benefit of these intensive glucose control practices in this environment, probably because these
The NICE-SUGAR encountered major criticisms: 12
- The use of different target ranges for blood glucose in the control and interventional groups (7.7-10 mmol/l vs 10-11.9 mmol/l in Leuven studies
- Different routes for insulin administration; types of infusion system used
- Difference in sampling sites
- Different glucometers used and difference in nutritional strategies.

Despite these criticisms, this trial contradicted and over- rode the trend towards IGC in the ICU that began with the earlier Leuven trials. Therefore, in view of the detrimental effects shown by NICE-SUGAR trial, IGC cannot be generally recommended for all ICUs. Although the ideal target glucose remains unclear, the standard of care in many medical and surgical ICUs targets 7.7-10 mmol/l. In fact, several guideline-issuing bodies recommend CGC:
- The 2012 Surviving Sepsis Campaign recommends a glycaemic target of ≤ 10 mmol/l in patients with severe sepsis.19

**Table 1:** Summary of intensive/tight glucose control studies.

<table>
<thead>
<tr>
<th>Study</th>
<th>Study synopsis</th>
<th>Results</th>
<th>Outcome</th>
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<tbody>
<tr>
<td>Leuven Surgical Trial17</td>
<td>In a surgical ICU, IGC (targeting a blood glucose of 4.4-6.1 mmol/l) was compared to CGC (targeting a blood glucose of 10-11.1 mmol/l), particularly amongst patients who were in the ICU for &gt; 5 days.</td>
<td>Decrease in ICU morbidity and lower incidence of systemic infections, acute renal insufficiency, anaemia, polyneuropathy, duration of artificial ventilation, and length of stay in the ICU.</td>
<td>Tight glucose control recommended.</td>
</tr>
<tr>
<td>Griesdale et al13</td>
<td>A meta-analysis of 26 RCTs involving a total of 13 567 patients, intensive insulin therapy was compared to conventional insulin therapy in the ICU.</td>
<td>Even though intensive insulin therapy significantly increased the risk of hypoglycaemia and conferred no overall mortality benefit among critically ill patients. This therapy, however, may be beneficial to patients admitted to a surgical ICU.</td>
<td>Tight glucose control may be beneficial to patients admitted to a surgical ICU.</td>
</tr>
<tr>
<td>Wiener et al14</td>
<td>A meta-analysis of 34 RCTs totalling 8 432 patients, intensive insulin therapy was compared to conventional insulin therapy in the ICU.</td>
<td>Hospital mortality did not differ between IGC versus CGC. Even though IGC was associated with an increased risk of hypoglycaemia, it was also associated with a decreased risk of septicemia.</td>
<td>Tight glucose control may be considered to decrease risk of septicemia.</td>
</tr>
<tr>
<td>Scalea et al15</td>
<td>Examined the impact of IGC policy on outcomes (from a 24 month period before the implementation of IGC protocol to a 24 month post intervention phase) associated with hyperglycaemia in critically injured patients.</td>
<td>IGC group falls in the improving pattern of glucose control, and a decrease from 29% to 21% in the incidence of early infection (develop in first 2 weeks) was observed after introduction of their tight glucose control protocol.</td>
<td>Tight glucose control may be considered.</td>
</tr>
<tr>
<td>NICE-SUGAR multicentre trial.16</td>
<td>NICE-SUGAR randomised 6 104 medical and surgical ICU patients to IGC (targeting a blood glucose of 4.5-6 mmol/l) versus CGC (targeting a blood glucose of ≤10 mmol/l).</td>
<td>Increased mortality among medical and surgical ICU patients who received IGC.</td>
<td>Tight glucose control not recommended.</td>
</tr>
<tr>
<td>VISEP multicentre trial.17</td>
<td>Designed to assess the efficacy of fluid resuscitation and of blood-glucose control (IGC versus usual care) in patients with severe sepsis and septic shock. In this study, blood glucose targets were 4.4-6.1 mmol/l and 10-11.1 mmol/l for the intensive and control groups respectively.</td>
<td>The study had to be stopped early after the incidence of hypoglycaemia (12.1%) in the IGC group was considered unacceptably high.</td>
<td>Tight glucose control not recommended.</td>
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Blood glucose measurement

To measure point-of-care blood glucose, two common procedures are used: venous or arterial blood by way of an intravascular catheter and capillary blood/ finger prick. Venous or arterial blood sampling is not only time-consuming but it also carries a risk of infection and involves a relatively large amount of blood drawn. Finger prickling, however, is prone to measurement errors, as shown in a study by Ting C and Nanji AA.22 In their study, they found that as many as 62% of values obtained in ICUs deviate from the reference laboratory values by >20%. Another study23 showed that in shock patients, only 36% of patients had finger stick-derived capillary glucose levels within 20% of the measured reference. These discrepancies in glucose levels...
Thus, mortality and morbidity may possibly be reduced by the chance of avoiding and glycaemic control could be improved. Having this information, hypo- or hyperglycaemic excursions and predictive alarms for low or high blood glucose levels. 3-7 days and they also have user-set alarms for rate of change of blood glucose over a period of several days. These systems have a sensor life which varies between these devices which provide continuous or near continuous monitoring capabilities, give “real-time” glucose readings, thus allowing immediate therapeutic adjustments. Glucose levels are continuously reported from a small electrode inserted into interstitial fluid under the skin, usually in the abdomen or upper arm. Almost all the subcutaneous CGM devices on the market utilise comparable glucose-oxidase methodology of glucose measurement and derive their results from interstitial fluid glucose, converted by a specific algorithm to reflect blood glucose.24 CGM equipment is typically worn by the patient for 3 to 5 days, and is especially useful for detecting nocturnal hypoglycaemia or dawn phenomenon and postprandial hyperglycaemia, which can be missed by other methods of blood glucose monitoring, and hence may have an advantage over “point-of-care” testing.

Designed to successfully improve glucose control, CGM provides information about glucose concentration, directional trends and rate of change of blood glucose over a period of several days. These systems have a sensor life which varies between 3-7 days and they also have user-set alarms for rate of change and predictive alarms for low or high blood glucose levels. Having this information, hypo- or hyperglycaemic excursions can be avoided and glycaemic control could be improved. Thus, mortality and morbidity may possibly be reduced by the prevention of newly acquired kidney injury, faster weaning from mechanical ventilation and accelerated discharge from the ICU.

### Accuracy of continuous glucose monitoring devices in the ICU

Although it seems to be a cost effective technology, the major disadvantage of CGM, however, is that the accuracy is not equivalent to that of glucose meters, as there is a physiologic lag between blood and interstitial space glucose of approximately 5 to 10 minutes and this lag is accentuated when glucose levels are undergoing rapid change.25 Even though some studies27,28 have demonstrated a reasonable correlation between abdominal interstitial fluid and arterial blood glucose measurements in critically ill patients in the ICU, glucose levels in the abdominal subcutaneous interstitial fluid may be affected by local blood flow and temperature (which may be substantially affected by manifestations of critical illness, such as shock, sepsis, or external cooling), the dynamics of systemic blood glucose changes, and the distance between the sensor and the blood vessel supplying the area of interest29 thus creating a major bias in glucose assessments. In fact, the relationship of interstitial fluid to blood in the critically ill patient, has been investigated only to a limited degree. Most of these studies30-37 have evaluated the accuracy of CGMs and address specific critical concerns such as hypotension, use of inotropes, hypothermia, oedema, renal and hepatic failure, hyperinsulinaemia, and acidosis. However, these studies were small and generally not powered to assess each of those variables.

Table 2 shows the different studies evaluating the accuracy of CGMs and their conclusions. Most studies showed that the accuracy of CGMs is not affected by the presence of oedema, hypotension, hypothermia, ketosis or inotropic support.30-32,34-36 However, hyperinsulinaemia itself reduced sensor glucose compared with venous glucose readings by about 20% in humans.35 In a study by Holzinger et al,38 real-time interstitial fluids CGM was compared with point-of-care blood glucose measurements to guide intravenous insulin infusion over 72 hours in 124

<table>
<thead>
<tr>
<th>Author(s)</th>
<th>Year</th>
<th>Condition of the patient</th>
<th>n</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lorencio et al30</td>
<td>2012</td>
<td>Patients on insulin therapy.</td>
<td>41</td>
<td>Accuracy was significantly better in patients with septic shock in comparison with the other patient cohorts.</td>
</tr>
<tr>
<td>Holzinger et al31</td>
<td>2009</td>
<td>Patients on inotropic support.</td>
<td>50</td>
<td>No interference in accuracy of CGM devices with inotropic therapy.</td>
</tr>
<tr>
<td>Price et al32</td>
<td>2008</td>
<td>Patients on inotropic support.</td>
<td>17</td>
<td>No interference in accuracy of CGM devices with inotropic support.</td>
</tr>
<tr>
<td>De Block et al33</td>
<td>2006</td>
<td>Septic shock, renal failure and patients on inotropic support.</td>
<td>50</td>
<td>Compared with patients on no inotropes and in those without renal failure and septic shock, the accuracy is worse in patients on inotropic support and better in renal failure and septic shock.</td>
</tr>
<tr>
<td>Pfützner et al34</td>
<td>2006</td>
<td>Patients with ketosis.</td>
<td>12</td>
<td>No interference in accuracy of CGM devices in ketosis patients when compared with patients without ketosis.</td>
</tr>
<tr>
<td>Piper et al35</td>
<td>2006</td>
<td>Patients with oedema, hypothermia, and on inotropes.</td>
<td>20</td>
<td>No interference in accuracy of CGM devices in such patients when compared with the other patient cohorts.</td>
</tr>
<tr>
<td>Goldberg et al36</td>
<td>2004</td>
<td>Oedema, hypotension and patients on inotropic support.</td>
<td>21</td>
<td>No interference in accuracy of CGM in such patients when compared with patients without oedema, hypotension and inotropic support.</td>
</tr>
<tr>
<td>Monsod et al37</td>
<td>2002</td>
<td>Hyperinsulinaemia</td>
<td>11</td>
<td>Interference in accuracy of CGM devices with hyperinsulinaemia.</td>
</tr>
</tbody>
</table>

CGM: Continuous glucose monitoring.
patients on mechanical ventilation. They found that real-time CGM reduces hypoglycaemic events but does not improve glycaemic control compared with intensive insulin therapy guided by an algorithm. A randomised study by Mraz et al. showed that CGM provided better glycaemic control without hypoglycaemia in comparison with standard monitoring to manage glycaemia in an intensive insulin treatment protocol. In another study, Tonyushkina et al. showed that 97% of readings in CGM patients were clinically acceptable with no episodes of hypoglycaemia over 24 hours, whereas hypoglycaemia occurred in 50% of patients in the control group. However, Rabiee et al. found that the CGM generally overestimated the actual serum glucose and missed 50% of the 30 actual hypoglycaemic episodes as determined by their glucometer, leading the authors to conclude that it was not sufficiently safe to be used in an ICU setting. Based on the limited available data related to accuracy of CGM devices, the Endocrine Society (USA) clinical practice guideline on CGM does not recommend the use of CGM in ICU settings where patients are unable to provide feedback about hypoglycaemic symptoms. They concluded that the potential danger in their use in guiding insulin administration in an acute care setting outweighs the possible convenience and trend awareness that the technology provides.

The future of continuous glucose monitoring devices: intravascular sensors

Automated blood glucose measurement systems that reside in the peripheral vein are under development and may be more accurate than the current FDA-approved CGM systems that monitor glucose via interstitial fluid. This will probably minimise the sources of bias of capillary and interstitial fluid glucose typically encountered in critically ill patients; not to mention that it will also minimise risk of contamination and infection involved in repetitive sampling from indwelling vascular catheters and also reduce medical personnel workload. In their porcine model, Skjaervold et al. reported preliminary data on a novel indwelling vascular continuous glucose sensor (which detects blood sugar fluctuations over a wide range. From less than 1 mmol/L to more than 15 mmol/L) by employing a unique hydrogel matrix that changes size continuously in relationship to ambient glucose concentrations, thus providing ongoing real-time reporting of results. This technology, research and concept have paved a way towards safer avenues to glucose control in our ICUs. Until the clinical benefit and safety of such state-of-the-art glucose management systems is clearly demonstrated in human studies, CGM will, however, not be ready for use in glucose control protocols in the ICU.

Conclusion

The technology of CGM devices provides a valuable and rapidly progressing area of research to determine whether or not the application of such novel devices will be sufficient for use with intensive insulin therapy in the ICU population. Even though the use of CGM appears promising, it must undergo a larger testing in the ICU setting before it can be used for implementation of tight glucose control policies in the ICU. Further development of long-term implantable sensors for measuring glucose continuously or as a “real-time” glucose vascular sensor, CGM technology could ultimately prove to be a blessing in the ICU, by decreasing medical personnel workload and by providing alarm signals for impending glycaemic excursions. RCTs examining the use of these new technologies to achieve tight glycaemic control while minimising the risk of hypoglycaemia would, however, still be necessary prior to adopting these devices in critical care.

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Conflicts of interest

The authors certify that there are no actual or potential conflicts of interest linked to continuous glucose monitoring devices in relation to this article.

References


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References