OBSERVATION

Glycemia management in critical care patients

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Abstract

Over the last decade, the approach to clinical management of blood glucose concentration (BGC) in critical care patients has dramatically changed. In this editorial, the risks related to hypo, hyperglycemia and high BGC variability, optimal BGC target range and BGC monitoring devices for patients in the intensive care unit (ICU) will be discussed. Hypoglycemia has an increased risk of death, even after the occurrence of a single episode of mild hypoglycemia (BGC < 80 mg/dL), and it is also associated with an increase in the ICU length of stay, the major determinant of ICU costs. Hyperglycemia (with a threshold value of 180 mg/dL) is associated with an increased risk of death, longer length of stay and higher infective morbidity in ICU patients. In ICU patients, insulin infusion aimed at maintaining BGC within a 140-180 mg/dL target range (NICE-SUGAR protocol) is considered to be the state-of-the-art. Recent evidence suggests that a lower BGC target range (129-145 mg/dL) is safe and associated with lower mortality. In trauma patients without traumatic brain injury, tight BGC (target < 110 mg/dL) might be associated with lower mortality. Safe BGC targeting and estimation of optimal insulin dose titration should include an adequate nutrition protocol, the length of insulin infusion and the change in insulin sensitivity over time. Continuous glucose monitoring devices that provide accurate measurement can contribute to minimizing the risk of hypoglycemia and improve insulin titration. In conclusion, in ICU patients, safe and effective glycemia management is based on accurate glycemia monitoring and achievement of the optimal BGC target range by using insulin titration, along with an adequate nutritional protocol.

INTRODUCTION

Over the last decade, the approach to clinical management of blood glucose concentration (BGC) in critical care patients has dramatically changed. Traditionally, BGC management in patients admitted to intensive care units (ICU) was mostly overlooked and "permissive" hyperglycemia was the standard of care[1,2]. In 2001, Van den Berghe *et al*[3] published the results of an innovative approach that tested a more aggressive management and proposed intensive insulin infusion therapy (IIT) targeted to tight BGC control (80-110 mg/dL). A few years later, it became clear that this approach carries the risk of increased frequency of hypoglycemia[4-6]. Subsequently, the

NICE-SUGAR study has demonstrated that moderate BGC control (140-180 mg/dL) is associated with lower mortality and a lower risk of hypoglycemia when compared to tight BGC[7].

In this editorial, the risks related to hypo, hyperglycemia and high BGC variability, optimal BGC target range and BGC monitoring devices for patients in ICU will be discussed.

RISKS RELATED TO HYPOGLYCEMIA

Hypoglycemia is related to an increased risk of death, even after a single episode of mild hypoglycemia occurs, and to an increase in ICU length of stay (LOS) (Table 1). In an observational study of 4946 ICU patients treated with moderate BGC control (target BGC range 108-180 mg/dL), at least 1 episode of hypoglycemia (BGC < 81 mg/dL) in 1109 patients was recorded[8]. In this study group, patients that developed hypoglycemia were at higher risk for mortality compared to those who did not (death 36.6% *vs* 19.7%, *P* < 0.05). It is important to underscore that even episodes of mild hypoglycemia (BGC 72-81 mg/dL) were associated with higher hospital mortality: 25.9% *vs* 19.7%, *P* < 0.05.

In a retrospective analysis of prospectively collected data in 6240 patients admitted to ICU, focused on the association between hypoglycemia (defined as BGC < 70 mg/dL) and LOS, these variables were consistently related, with dose-response and episode-based having a linear predictive value[9]. In patients without hypoglycemia compared to those with a single episode, ICU median interquartile LOS was 1.8 (1-0-3.3) *vs* 3.0 (1.5-6.7) d, *P* < 0.0001. The relationship between hypoglycemia and LOS was independent of the severity of illness and survivor status. The authors concluded: "Successful avoidance of hypoglycemia has the potential to significantly decrease the cost of care of the critically ill". The LOS is the predominant measure of resource utilization in critical care patients. Various studies have provided evidence on costs savings related to preventing hyperglycemia because of decreased LOS, infections, pharmacy, laboratory and imaging use[10]. Also, the prevention of hypoglycemia can contribute to the reduction of LOS and ICU costs.

RISKS RELATED TO HYPERGLYCEMIA

Hyperglycemia, with a threshold value of 180 mg/dL, relates to an increased risk of death, LOS and morbidity due to infection in ICU patients. In a retrospective chart review of 210 patients assigned to moderate BGC control (target range 80-140 mg/dL) or with an uncontrolled BGC regimen, patients assigned to the latter group treatment had a higher mortality (5% *vs* 18%, *P* < 0.01)[11,12]. Mean BGC values higher than 181 mg/dL were associated with an increased risk of death: OR = 1.3, 95% CI: 1.1-1.6; *P* = 0.01. The increased mortality related to hyperglycemia is confirmed by data on BGC at ICU admission in 5828 medical/surgical ICU patients[13].

Table 1 Risks related to hypo, hyper glycemia and high blood glucose target range variability

Take home message
Hypoglycemia is clinically relevant, increased mortality and LOS for BGC values < 80 mg/dL
The risk of hypoglycemic episodes is related to: BGC target range; insulin infusion duration
Hyperglycemia is clinically relevant, increased mortality, increased LOS and higher incidence of postoperative infections for BGC values > 181 mg/dL
High glycemia variability and high complexity of glycemic profile are associated with increased mortality rate

BGC: Blood glucose concentration; LOS: Length of stay.

In this study, cohort data were divided into quintiles of increasing mean BGC and the results demonstrated that mean BGC at ICU admission is related to mortality by a "U-shaped" curve, values < 120 mg/dL and > 162 mg/dL were associated with increased risk of death: OR 2.4 (1.4-4.0) and 3.0 (1.8-5.1); *P* < 0.001.

A similar trend, with "U-shaped" relationship links mean glucose concentration during the first 24 h after surgery and the incidence of postoperative infections, as reported in a retrospective analysis of a sample of 55 408 diabetic patients that underwent non cardiac procedures[14]. In those patients with a mean 24 h serum glucose 150 to 250 mg/dL, the incidence rate ratio was 1.22, 95% CI: 1.04-1.43, *P* = 0.01. Of interest, in this study group the values of preoperative serum glucose concentration and hemoglobin A1c were not associated with an increased risk of postoperative infections, suggesting that was not the quality of preoperative glycemia control that determined the increase in infection rate.

RISKS RELATED TO HIGH BGC VARIABILITY

High serum glucose variability and differences in complexity of the glycemic profile predicts increased risk of death in ICU patients.

Risk related to BGC variability as a predictor of mortality in an ICU population was initially presented by Krinsley and demonstrated how standard deviation (SD) within different ranges of mean glycemia is associated with increased death rate[15]. However, SD is not the most appropriate statistical approach to measure the extent of BGC variability[16]. In a retrospective analysis in 5728 ICU patients, treated with a computerized-based sliding-scale IIT targeted to BGC 72-126 mg/dL target range, the mean absolute glucose change (MAG) per patient per hour (that is a function of BGC absolute changes and time spent in ICU) was associated with ICU death in the low and high ranges of BGC: OR 4.1, 95% CI: 1.9-9.1; *P* < 0.001[17]. The MAG values were more tightly associated with mortality rate than SD of median BGC; median SD was 32 mg/dL and median MAG was 11 mg/dL; thus

qualifying this approach to evaluate changes in glycemia variability. Results from this study have also further demonstrated how hyperglycemia is harmful, since when high MAG was associated with high mean BGC (highest quartile), the highest mortality rate was recorded: OR 12.4, 95% CI: 3.2-47.9; $P = 0.001$. This evidence was confirmed in a prospective study in 48 ICU patients where a continuous measure of subcutaneous interstitial fluid glucose levels were recorded every 5 min for 48 h[18]. In these patients, the complexity of glycemic profile was evaluated by detrended fluctuation analysis (DFA) and resulted in significantly lower values in survivors compared to non-survivors: 1.49 (CI: 1.44-1.53) *vs* 1.60, $P = 0.015$. Of interest in this study, patients age, gender, simplified acute physiological score 3 and Acute Physiology and Chronic Health Evaluation II scores, type of feeding (oral, enteral or parenteral) and amount of insulin infused were not associated with differences in DFA.

According to this evidence, it is important to minimize sudden changes in BGC and therefore to avoid insulin bolus injections, both intravenous and subcutaneous, and to prevent the infusion of solutions containing high glucose concentration that are sometimes prescribed to correct iatrogenic induced hypoglycemia.

OPTIMAL BGC TARGET RANGE

Over time the optimal BGC target range has dramatically changed[19]. Available evidence now suggests that a tailored BGC target range should be adopted in specific subgroups of patients and might be corrected according to the nutrition protocol used and depending on the duration of insulin infusion. According to the NICE-SUGAR data results, as mentioned in the introduction section, there is no additional benefit from lowering BGC levels below a "moderate" target range (140-180 mg/dL); this range is associated with lower 90 d mortality compared to "tight" BGC (target range 80-110 mg/dL) and to a lower risk of severe hypoglycemia.

This evidence was in part challenged by 2 retrospective reviews that analyzed data in trauma patients. In 2008, patients survival rate before and after the implementation of tight BGC control protocol (standard BGC target range 80-200 mg/dL *vs* tight BGC target range 80-110 mg/dL) resulted into a significant improvement in those aged 41 to 50 years and 51 to 60 years: 21/131 (18.3%) *vs* 20/226 (8.8%); $P = 0.009$ and 24/86 (27.9%) *vs* 26/181 14.4%; $P = 0.08$[20]. Data from 1422 trauma patients when retrospectively divided into 3 non-overlapping, sequential treatment groups according to the protocol used for BGC control (relaxed: BGC target range <180 mg/dL; aggressive: BGC target range 80-120 mg/dL; and moderate: BGC target range 80-140 mg/dL), demonstrated that a "moderate" approach balanced maintenance of normoglycemia, reduction in glucose variability and minimization of hypoglycemic and hyperglycemic events, while maintaining equivalent outcomes when compared with a more aggressive strategy[21]. This

study also confirmed that hyperglycemic events (BGC > 180 mg/dL) most strongly predicted mortality. The optimal BGC target range is not yet established and the authors of this study commented: "Additional rigorous studies would be needed to identify the specific normoglycemic ranges and protocol adjustment and monitoring characteristics required to achieve target glucose level". In a prospective nested cohort study in 523 medical/surgical ICU patients assigned to 1 out of 6 BGC target range group treatments (group1 BCG < 108 mg/dL; group 2 BGC 108-114 mg/dL; group 3 BGC 115-128 mg/dL; group 4 BGC 129-145 mg/dL; groups 5 BGC 146-181 mg/dL; group 6 BGC > 181 mg/dL), the 129-145 mg/dL target range was associated with the lowest mortality rate[22]. The authors concluded that targeting BGC to < 146 mg/dL ("advanced BGC target range: 129-145 mg/dL) is associated with less risk of inadvertent hypoglycemia and represents an optimal BGC level in critically ill patients.

The target BGC level is not the only variable that affects the relationship between insulin infusion, the risk of iatrogenic hypoglycemia and ICU outcome. Among the most relevant variables that contribute to determine the effects of insulin infusion on BGC are: the nutritional protocol, duration of insulin infusion and the changes in insulin sensitivity over time.

A systematic review and meta analysis of the effects of tight BGC control (80-110 mg/dL) in ICU patients showed that this approach does not reduce 28 d hospital mortality, incidence of blood stream infections or requirement for renal replacement therapy[23]. The authors also recorded that IIT may be harmful in patients receiving enteral nutrition; however, it appears to improve the outcome of patients receiving the majority of their carbohydrate load parenterally. The duration of insulin infusion is a predictor of severe hypoglycemia (BGC < 40 mg/dL), as demonstrated in a retrospective analysis in 1118 ICU surgical patients treated with tight BGC (target BGC 80-110 mg/dL)[24]. This study confirmed the increased odds for death among patients even after a single episode of hypoglycemia (26.9% *vs* 15.3%, $P = 0.03$) and showed how occurrence of severe hypoglycemia does not reflect illness severity or demographic features but is related to the time of insulin infusion. The relationship of length of insulin infusion can be possibly explained by the induced changes in insulin sensitivity.

According to available evidence, state-of-the-art BGC management in ICU patients should be addressed to maintain glycemia within 140-180 mg/dL target range (NICE-SUGAR). More recent evidence suggests that a lower target range 129-145 mg/dL is associated with the lowest mortality rate as compared to other treatment groups. In some subgroups of patients, "dedicated" target ranges might have clinical benefits. In trauma patients without traumatic brain injury[25], "moderate" BGC management (BGC target range 80-140 mg/dL) or "tight" BGC management (BGC target range 80-110 mg/dL) in the 41-60 year age group is associated with reduced

mortality. Safe BGC targeting and estimation of optimal insulin dose titration should include an adequate nutrition protocol, the length of insulin infusion and the change in insulin sensitivity over time.

BGC MONITORING

Critical care control of BGC necessitates frequent and accurate monitoring to avoid hypoglycemia and inadequate insulin titration[26]. Traditionally, clinical glucose measurements are based on central laboratory devices and point of care (POC) devices. The POC devices, although potentially attractive because of ease of handling and rapid results, are not suitable in ICU patients due to inaccuracy (differences in results exceeding 20% of a reference value)[26]. Besides issues related to POC device accuracy, it is important to recall that several clinical and laboratory variables, including inadequate cardiac output, arterial hypotension, hypoxia, hematocrit values, pH, associated therapies etc., can interfere with BGC measurement accuracy[26,27]. These issues have driven the need for real time continuous glucose monitoring (CGM) devices[28]. Recently, an intravascular CGM sensor has been tested in the preclinical setting with promising results[29,30]. The CGM can possibly contribute, not only to minimizing the risk of hypoglycemic events and to optimize insulin titration, but also to provide information on BGC variability and trends. These variables are possible predictors of outcome in ICU patients[31].

CONCLUSION

In critical care patients, hypo, hyper and high BGC variability are associated with an increased risk of death. The relationship between mean BGC and mortality is described by a "U-shaped" curve, with lower and higher BGC values associated with higher death rate. Similarly, increased rates of BGC variability and complexity of glycemic profiles relates to higher ICU mortality.

It is clinically relevant to underline that even mild hypoglycemia (BGC < 80 mg/dL) is associated with an increased risk of death; this value should therefore be considered the lower threshold for safe BGC management in ICU patients. The higher glycemia threshold is 180 mg/dL; values that exceed this level are associated with increased morbidity and mortality. Preventing hypoglycemia and hyperglycemia can also effectively contribute to reduce LOS and ICU costs. As much attention that is spent to prevent hypo and hyper glycemia should be used to minimize changes in BGC variability. Therefore, bolus insulin injection, both intravenous and subcutaneous, and bolus infusion of high glucose concentration solutions should be strictly avoided (Table 2).

State-of-the-art for glucose target range encompasses insulin infusions aimed at maintaining BGC within 140-180 mg/dL range. Recent evidence suggests that lower BGC target range (129-145 mg/dL) is safe and effective in ICU patients. In trauma patients without trau-

Table 2 Practical tips for blood concentration
Take home message
Avoid injecting insulin boluses, both subcutaneous **and intravenous**
Avoid infusing high glucose concentration solution
Avoid point of care devices for BGC measurements
Use parenteral nutrition
In ICU patients
"Standard", according to the "state-of-the-art" BGC target range: 140-180 mg/dL
"Advanced" BGC target range: 129-145 mg/dL
In trauma patients (without traumatic brain injury):
Overall: BGC < 140 mg/dL
If aged 41-60 years: 80-110 mg/dL

BGC: Blood glucose concentration; ICU: Intensive care unit

matic brain injury, moderate BGC (target < 140 mg/dL) is associated with reduced mortality.

Continuous glucose monitoring devices that provide accurate measurement can contribute to minimizing the risk of hypoglycemia and improving insulin titration.

In conclusion, in ICU, a patient's safe and effective glycemia management is based on accurate glycemia monitoring, achieving optimal BGC target range and insulin titration, along with an adequate nutritional protocol.

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