TOPICS

- Association between hyperglycemia and mortality in ICU
- Intensive insulin treatment seems to have a significant benefit for surgical ICU patients
- New ways for targeted glycemic control with a minimized risk of hypoglycemia

INTRODUCTION

There is a substantial body of evidence demonstrating that uncontrolled hyperglycemia is associated with an increase in morbidity and mortality in a variety of clinical settings. Although several studies have shown that strict glucose control in conjunction with intensive insulin therapy can reduce morbidity and mortality in critically ill patients, other trials found that a wider blood glucose target range may be beneficial. New technologies and intelligent computer algorithms may help to implement tight glycemic control with a reduced risk for hypoglycemia. The new Space GlucoseControl is a decision-support system which may help to achieve safe and reliable blood glucose control in the two target ranges 4.4mmol/l to 6.1mmol/l and 4.4mmol/l to 8.3mmol/l.

Effective and safe glucose control

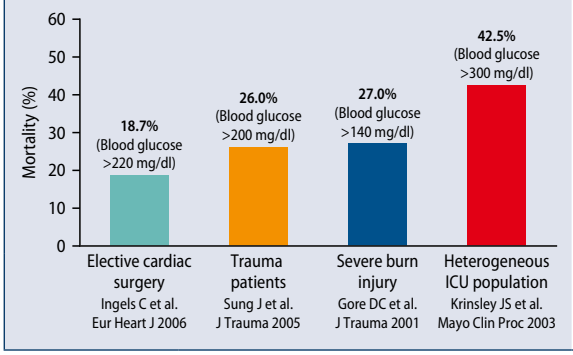
Glucose management in intensive care units

Tight glycemic control has been implemented as a lifesaving strategy in many intensive care units (ICUs) around the world. The landmark Leuven study [1] demonstrated that tight blood glucose control and intensive insulin therapy which were targeted to maintain normoglycemia between 80mg/dl and 110mg/dl (4.4mmol/l and 6.1mmol/l) reduced mortality in the surgical ICU. However, there is still some controversy about this theme. Thus, recent multicenter studies such as the Volume Substitution and Insulin Therapy in Severe Sepsis (VISEP) [2] and the NICE-sugar trial [3] did not confirm the survival benefit of intensive versus conventional glucose control seen in the Leuven study.

In principle, the need to maintain euglycemia in the ICU has been widely accepted. There is a strong association between hyperglycemia and mortality (**Fig. 1**). In patients undergoing elective cardiac surgery, mortality increases to 18.7% with blood glucose exceeding 220mg/dl [4]. Similar results were found in trauma patients [5] and in patients with severe burn injuries [6]. In a heterogeneous group of critically ill patients it was shown that even a modest degree of hyperglycemia was associated with a substantial increase in mortality: Hospital mortality increased progressively as glucose values increased, reaching 42.5% among patients with mean glucose values exceeding 300mg/dl [7].

In the past few years, several mechanisms of harm implicated in hyperglycemia have been identified. High levels of circulating blood glucose are toxic, especially at cellular levels (**Fig. 2**). The clinical consequences of these cellular changes are altered immunity and impaired wound healing, as well as an increase in inflammation, sepsis and possibly multiorgan failure [8].

Figure 1



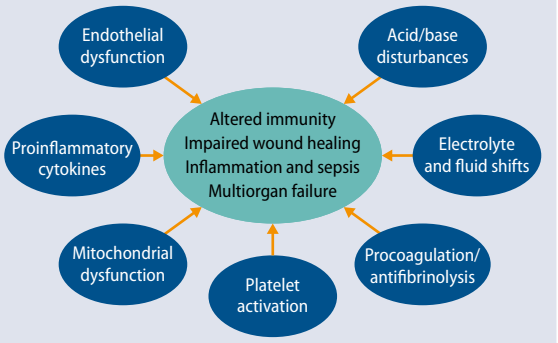
Association between hyperglycemia and mortality

modified from [4, 5, 6 7]

Randomized controlled trials of strict glucose control

The Leuven trial was the first study which demonstrated that intensive insulin therapy in critically ill patients is associated with an improved outcome [1]. It was carried out as a single-center randomized controlled trial and enrolled 1,548 surgical ICU patients; 63% of the population had undergone cardiac surgery. These patients were randomized to receive either intensive insulin treatment to a target range of 80mg/dl to 110mg/dl (4.4mmol/l to 6.1mmol/l) or conventional treatment to a target range between 180mg/dl and 200mg/dl (10.0mmol/l and 11.1mmol/l), if blood glucose raised above 215mg/dl (11.9mmol/l). After 12 months, intensive insulin therapy reduced ICU-mortality from 8.0% in the conventionally treated group to 4.6% in the intervention group (relative risk reduction 42%, p=0.04). In-hospital mortality was reduced from 10.9% to 7.2% (relative risk reduction 34%). Patients who stayed more than five days in the ICU had the greatest survival benefit (20.2% with conventional treatment versus 10.6% with intensive insulin therapy, p=0.005). In addition to the decrease in mortality the authors found marked reductions in the incidence

Figure 2



Mechanisms of harm in hyperglycemia

modified from [8]

of sepsis (-34%), in the need for hemodialysis (-41%) and blood transfusion (-50%), and in the incidence of critical-illness polyneuropathy (-44%) in the intensively treated patients.

Subsequently, some smaller studies confirmed the beneficial results of strict glycemic control in critically ill patients, particularly in pa-tients with cardiac surgery. However, recent multicenter studies such as the VISEP study did not confirm a survival benefit [2]. The VISEP trial was a multicenter study with septic patients. It was stopped prematurely for safety reasons, because it showed an increased incidence of severe hypoglycemia with tight glycemic control. At 28 days and at 90 days, there was no significant difference in mortality (24.7% and 39.0%, respectively, in the intervention group versus 26.0% and 35.4% in the control group) [2].

In the NICE-sugar study, a multicenter study from Australia, New Zealand and Canada, the 90 day mortality was 27.5% in the intensive-treatment group versus 25.9% in the control group (p=0.03) [3]. "The NICE-sugar study was the mirror image of the Leuven trial", said *Dieter Messotten, Leuven/Belgium*. Hypoglycemia was significantly more common in the intensive-treatment group (6.9% vs. 0.5%, p<0.001), but the excessive death seen in this study was due more likely to cardiovascular problems than to hypoglycemia. However, the results show that tight glycemic control is not without risk. It seems to be strongly associated with hypoglycemia in all of the multicenter studies. Patients who have obviously the highest risk for hypoglycemia are septic patients.

Differences in the methodology of blood glucose measurement

The comparison of the present data is complicated by huge differences in the methods of measuring blood glucose levels in the ICU, as Dieter Mesotten, Leuven/Belgium, stated. Thus, it is important whether the sample is taken from whole blood, plasma or serum. Plasma contains fewer lipids, proteins and cells and thus has a greater water content. Therefore, each volume of plasma contains more glucose than the same volume of whole blood. In plasma, the glucose content is about 11% higher than it is in whole blood. Furthermore, glycemia is highly dependent on the hematocrit. Low levels of hematocrit lead to high glucose values. In consequence, there is an overestimation of hyperglycemia in patients with anemia. Glycemia also depends on the source of the sample: In the arteries it is about 5mg/dl higher than in the capillary measurement, which itself is 5mg/dl higher than in venous measurements, explained Mesotten. Blood glucose meters show a high variability in methodology and are designed for the monitoring of blood glucose levels in diabetics in a home environment. But they are not accurate enough to keep blood glucose levels within the narrow range of tight glucose control in an ICU setting. "If you are doing tight glycemic control, you need more reliable methods," Mesotten emphasized. For tight glycemic control or any narrow target range of blood glucose in the ICU, capillary blood sampling as well as most POC (point of care) glucose meters are not adequate. So far, only measurement of arterial glucose and in a blood gas analyzer seems appropriate.

What are the explanations for the contradictory results?

Apart from the basic possibility that tight glycemic control in ICU patients may indeed not be beneficial, there are several methodological differences between the Leuven study [1] on the one hand and the VISEP and NICE-sugar stud-ies on the other hand, which may explain the conflicting results (**text box**). The Leuven study was a highly standardized single-center study. The nurses were specifically trained to do the tight glycemic control; the nurse-to-patients ratio was 1:2. Blood glucose measurement was done only from arterial lines, noted Messotten. The multicenter NICE-sugar study was more liberal in methodology: Most aspects of patient care were carried out at the discretion of the treating clinicians. There was no standardization in glucose measurement. Moreover, feeding strategies differed significantly between the two studies. In the Leuven study, patients were fed parenterally and enterally (1,100kcal/day) whereas patients in the NICE-sugar study were fed only enterally with a hypocaloric amount of 880 kcal/day. Therapy compliance was better in the Leuven study: The blood glucose target was reached in 70% of patients, in the NICE-sugar study in less than 50%.

The results of a recent meta-analysis on intensive insulin therapy and mortality among critically ill patients show that tight glycemic control may be beneficial in surgical patients [9]. The authors included 26 randomized clinical trials with a total of 13,567 patients. According to these data, the ICU setting is an important factor. Thus, the mortality in surgical ICU patients is significantly decreased by intensive insulin therapy (risk ratio 0.63; 95% CI: 0.44-0.91), whereas there was no effect in other ICU settings. The present data underscore the fact that the ability to correctly implement a glucose management protocol is a key prerequisite to successful and safe glucose control in critically ill patients.

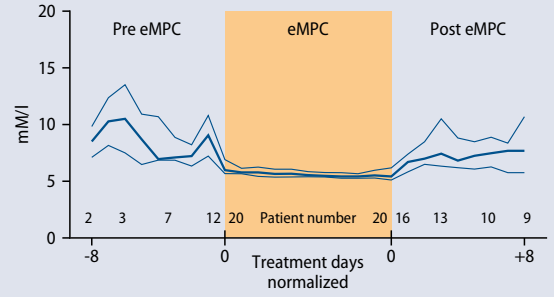
New ways for targeted glycemic control

Glucose control in the ICU is challenging, because it increases the workload for the physicians as well as for the nurses, noted *Karin*

Amrein, Graz/Austria. Tight glucose control is associated with an increased risk of hypoglycemia. Moreover, in an ICU setting, insulin requirements can vary in the same patients over time. The course of critical illness, use of steroids, use of hypothermia and the hepatic function play an important role in this setting. The current situation led to the initiation of the CLINICIP (Closed Loop Insulin Infusion for Critically Ill Patients) project, a European project in which many international partners collaborated. The project led to the development of the enhanced Model Predictive Control (eMPC) algorithm for glycemic control in critically ill patients, which has been incorporated into the Space GlucoseControl (SGC) system. This system helps to achieve safe and reliable blood glucose control in two desired ranges: 80mg/dl to 110mg/dl (4.4mmol/l to 6.1mmol/l) for a more strict glucose control and 80mg/dl to 150mg/dl (4.4mmol/l to 8.3mmol/ l) for moderate glucose control. Studies with the eMPC algorithm showed its high efficiency: Compared to standard protocols from four different European intensive care units, eMPC succeeded in keeping the blood glucose levels within the target range for a longer period of time (**Table 1**). The computer algorithm enables the SGC system to establish tight glycemic control with a minimized risk of hypoglycemia. The SGC system is based on the Space platform which consists of three infusion pumps for enteral nutrition, parenteral nutrition and an insulin pump. These three pumps are connected to the SGC interface, which contains the eMPC algorithm to calculate the appropriate insulin rates. The new system includes the blood glucose measurement, which is usually done by the nursing staff; the treatment algorithm; the infusion of enteral and parenteral nutrition; and the insulin therapy. In addition, it determines the next time of blood sampling, which is indicated via countdown timer and acoustic alarm. After the insulin rate and the sampling time have been confirmed by the ICU professionals, the device automatically administers insulin to the patient until the next sampling time. "Now there are no intuitive decisions needed," underscored Amrein.

A bedside laptop version of the eMPC algorithm was tested in a single-center study in a medical ICU [10]. Twenty mechanically ventilated patients with a mean age of 69 years and with an APACHE II score of 25.5 were included into the study. The mean treatment duration with the eMPC was 7.3 days. Time within target range (80mg/dl to 110mg/dl) was 58.12% ± 10.05%, the time within the extended target range (110mg/dl to 150mg/dl) was 23% ± 7%. So more than 80% of the time the blood glucose values were between 80mg/dl and 150mg/dl (4.4mmol/l and 8.3mmol/l). The mean arterial blood glucose level was 5.8mmol/l ± 0.5mmol/ l (**Fig. 3**), the insulin requirement was 101.3IU/day ± 50.7IU/day. Three hypoglycemic episodes (<2.2mmol/l) occurred in three different patients (15%), corresponding to an incidence of 0.02 per treatment day. "This rate is comparable to the hypocglycemia rate in other medical ICUs," said Amrein. The SGC system with the implemented eMPC system is currently being tested in several studies in both medical and surgical ICUs. Preliminary results from eleven severely ill patients (20 are planned) in a medical ICU show that 75% of glucose readings were within the target range of 80mg/dl to 150mg/dl (4.4mmol/l to 8.3 mmol/l). In these patients no hypoglycemic episodes occurred, Amrein emphasized.

Figure 3



The Space Glucose-Control system controls glucose and brings it close to normo-glycemic range

modified from [10]

Conclusion

Uncontrolled hyperglycemia is associated with an increase in morbidity and mortality in a variety of clinical settings. Tight glycemic control may be beneficial to patients treated in surgical ICUs, but it cannot be recommended generally for all ICUs, because it is associated with an increased risk for hypoglycemia. With regard to tight glycemic control, the balance between benefit and harm depends on the case mix, availability of staff and laboratory equipment, and feeding strategies. New technologies and intelligent computer algorithms such as the SGC system may help to implement tight glycemic control without the increased risk for hypoglycemia.

Table 1

Clinical eMPC studies: Percentage of time blood glucose levels were within target range of 80mg/dl –110mg/dl

	standard care	eMPC
Plank et al. 2006	19.0%	52.0%
Hovorka et al. 2007	27.5%	60.4%
Cordingley et al. 2009 ICU Leuven	63.4%	66.1%
Cordingley et al. 2009 ICU London	23.5%	57.2%

modified from [11, 12, 13]

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Interview with Karin Amrein, MD, Medical Intensive Care Unit, Medical University of Graz, Austria, on the present recommendations in blood glucose management in intensive care medicine (ICM).

Glucose management in ICM

In intensive care medicine, the control of blood sugar levels becomes more and more a focus of the discussions. What is this all about?

Amrein: The team around Greet van den Berghe conducted two monocenter trials in 2001 and 2006. They were able to show that strict glycemic control within the range of 80mg/dl to110mg/dl in surgical as well as medical intensive care patients who are staying longer in the ICU resulted in lower morbidity and mortality. That was a milestone. Unfortunately, further studies reported conflicting results.

In summary, in intensive care medicine there are various pieces of the puzzle which need to be put together for the complete picture in order to be able to ensure optimal care and safety for the patient. The control of blood glucose levels is one of them.

B.Braun is now launching Space GlucoseControl. Could you quickly explain what exactly this is?

Amrein: It is a decision-support system which aims to reduce the complexity of daily work in an intensive care unit by using technical support. An algorithm calculates the insulin rate to be infused, taking into account the actual blood glucose levels as well as nutrition being infused via gastric tube and/or parenterally. Furthermore, the next sampling time-point is calculated aiming to keep the blood glucose levels within defined borders.

You already have experience with Space GlucoseControl. What is your opinion about the new system?

Amrein: Currently, the system is used with conditions of a clinical study setting. That always means an additional workload compared to routine use. The data have not yet been analyzed, but we have the impression that the blood glucose control done with the SGC system is better. It is important that the system provide a certain comfort level to ensure acceptance by the nursing personnel. This is the prerequisite to achieving routine use.

And how does the SGC system affect the safety of patients and users?

Amrein: Without the system we would probably go for a less strict glycemic control. By using the SGC system with the actual target range of 80mg/dl to150mg/dl, the risk of hypoglycemia is low. In the currently ongoing study we have not seen any hypoglycemic episodes <40mg/dl so far.

How do the clinical studies with the system look?

Amrein: To date, there are clinical studies ongoing in medical as well as in surgical and cardio-surgical patients. The primary objective is the reliability of the algorithm; i.e., it is being tested whether the blood glucose levels are steadily within the target range. It is still open whether the short-term additional effort/workload of more frequent blood sampling eventually leads to an improvement in clinical outcome for the patient.

Do you think that such automation of processes in the ICU is a future scenario?

Amrein: We are experiencing a tremendous impact on the workload in the ICUs due to increasing complexity. An automation of routine processes results in support and safety of the therapies. It is important to stress that the last decision always has to be taken by trained nursing personnel with/without physicians.

With regard to glucose control, a sensor which measures blood glucose levels directly and uses the values immediately would be ideal. As well, further parameters could be measured in the same sample, such as electrolytes and oxymetry.

In the long run, I could imagine automation for further processes or alarm functions for continuously measured parameters such as the ventilation of patients or the adjustment of blood pressure. That might be the outlook for the next 20 years.

Imprint

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