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MEETING PROCEEDINGS

Tight Glycemic Control in the Hospital

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Abstract

Single center randomized controlled trials could demonstrate a benefit of strict glycemic control on the mortality and morbidity outcomes for critically ill patients. Although observational studies also demonstrate a benefit of tight glucose control for patients in general wards, direct evidence is still lacking. Overall, the implementation of glucose control both in the very controlled setting of an intensive care unit and even more so in the clearly less controlled setting of a general ward has proven to be difficult. Standardization of all required working steps to establish glycemic control needs to be considered to be able to achieve safe and good blood glucose control. Recent developments from diabetes technology will have an important impact in facilitating glucose control in the hospital, although the already established workflows in hospitals will require a substantial reconsideration of diabetes-oriented technology to allow an area-wide implementation and acceptance by health care personnel.

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Introduction

Over the past years, a paradigm shift in critical care with respect to blood glucose control has occurred due to the publication of two single center randomized controlled trials by Van den Berghe and colleagues.[1,2] In these studies, Van den Berghe was able to provide evidence that the normalization of blood glucose by intensive insulin therapy in patients at a surgical and a medical intensive care unit resulted in markedly improved survival for critically ill patients.

Revealing the exact current situation of glucose control for all inpatients, not only of patients requiring intensive care, seems of rising interest. It appears, however, that hospitals are, in general, very large and complex structures with mostly independent organized departments. It is therefore difficult to describe the quality of the implementation of a certain treatment regime in a hospital. In fact, results of clinical data available always relate to a certain department and, more importantly, also to very distinct patient populations representing very individual needs. For example, the Medical University Hospital Graz has 77 independently organized units and wards, (i.e., 58 general wards with ~1400 beds, 10 intensive care units with ~140 beds, and 9 emergency departments) in addition to 16 outpatient clinics.

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The following examples indicate blood glucose control during routine care as obtained from 10 patients in a surgical intensive care unit over a period of 2 consecutive days (**Figure 1A**),[3] 25 patients in a general medical intensive care unit over 3 consecutive days (**Figure 1B**),[4] and 5 patients in a general medical ward over 5 consecutive days (**Figure 1C**). Data reveal a major difference in the intensity of glucose control, i.e., between approximately three measurements per 24 hours per patient in a general medical ward to approximately nine measurements per patient per 24 hours at a surgical or medical intensive care unit. This major difference is also reflected in the median blood glucose concentration achieved, which was 7.1 and 8.4 m*M* in the surgical and medical intensive care unit with more frequent glucose controls vs 10.4 m*M* at a general medical ward with only approximately three glucose measurements per day.

The pivotal question now arises: *is there a need for improved glucose control in a general ward?* The answer is we do not know. No randomized controlled outcome study has been performed to date to answer this question. However, several observational studies have found a clear association between glucose concentrations and outcome. Based on these studies, most importantly on a study performed by Umpierrez and colleagues,[5] the position statement of the American Diabetes Association regarding standards for inpatient glucose control points toward the requirement of more strict glucose control also for patients in a general ward.[6] The position statement clearly suggests keeping the glucose as close to 6.1 m*M* as possible but at least below 10 m*M*.

The study by Umpierrez and associates[5] is based on an observational retrospective analysis of glucose control in 2020 patients in a general medical ward. The investigators found 7% of the patients without any record regarding glucose readings, 26% of the patients with a remark on a previous history of diabetes, and 12% of the patients with newly diagnosed hyperglycemia, which might be because of unrecognized diabetes, prediabetes, or stress associated with the hospital admission. The remaining 55% of the patients did not have an admission fasting glucose above 7 m*M* or at least no random glucose readings above 11.1 m*M* during the stay at the hospital. Applying multivariate odd ratios, Umpierrez *et al.*[5] found a significant and 2.7-fold risk of mortality for patients with known diabetes and an 18-fold risk of mortality for patients with new hyperglycemia. Although these numbers seem alarming, a causal link between poor glucose control and in-hospital mortality cannot be concluded from these data.

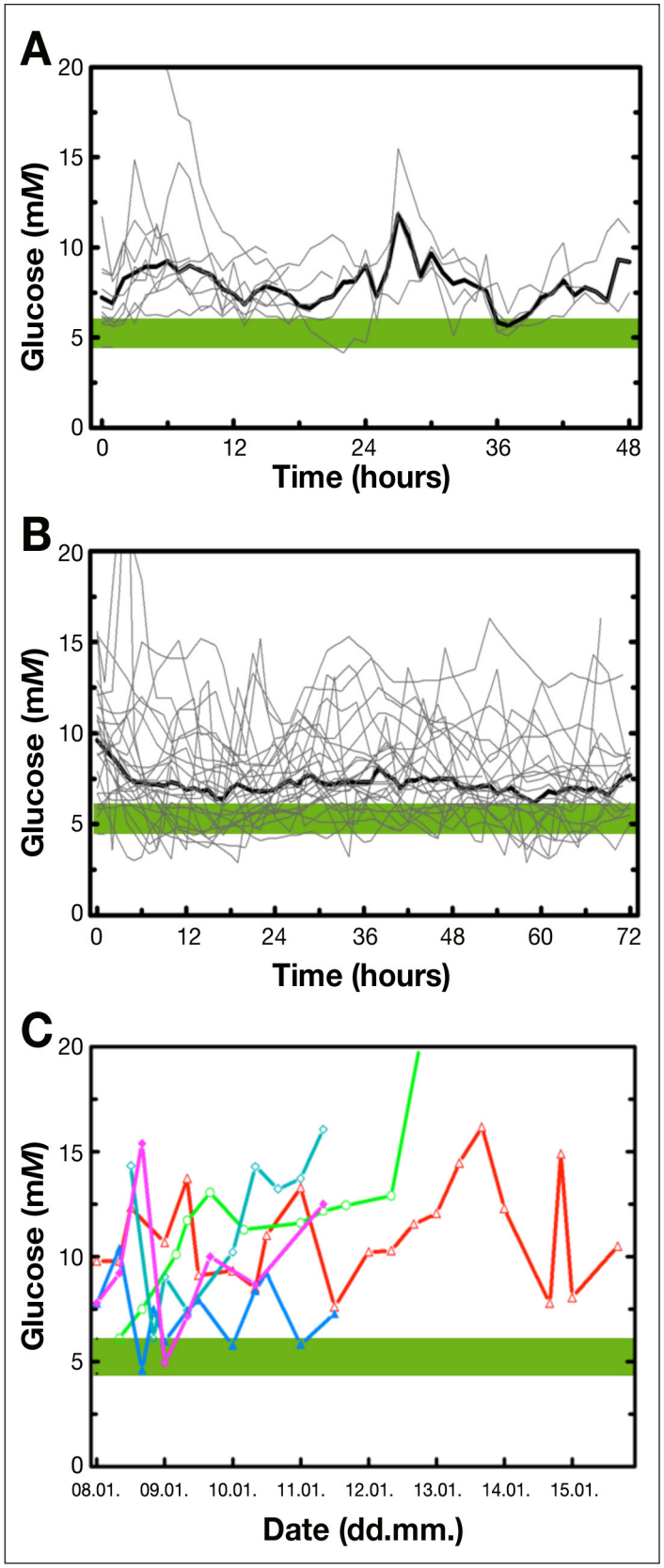

Figure 1. Blood glucose control during routine care as obtained from 10 patients in a surgical intensive care unit over a period of 2 consecutive days (**A**), 25 patients in a general medical intensive care unit over 3 consecutive days (**B**), and 5 patients in a general medical ward over 5 consecutive days (**C**).

In contrast to the situation in general wards, there is substantially more evidence available for patients in intensive care units. Two major randomized controlled trials, along with longitudinal observational studies, have indicated that the implementation of intensive insulin therapy brings a potential outcome benefit in terms of mortality and morbidity improvements for patients at various different intensive care units.[1,2] However, two multicenter randomized controlled trials performed on intensive care patients have failed and had to be stopped because of an increased risk of patients experiencing severe hypoglycemic events.[7,8]

In the study by Brunkhorst and colleagues,[7] 600 patients who developed sepsis were originally planned to be investigated in a multicenter setting in 17 regional centers. However, the study was stopped after 488 patients, with the major conclusion that intensive insulin therapy placed septic patients at an increased risk for serious adverse events related to hypoglycemia. This rather disappointing result makes it quite clear that the actual implementation of tight glucose control in an inpatient setting is very difficult to achieve, even if patients are in a rather well-controlled environment of an intensive care unit.

Why Is the Implementation of Glucose Control Difficult?

Glucose control is based on a relatively rapid feedback loop that has to be managed several times per 24 hours per patient. In most intensive care units, the nurse is responsible for running this loop, which starts with a glucose measurement, continues with the decision about the required infusion of a certain amount of insulin, and the decision when to perform the next blood glucose measurement (**Figure 2**). The development of guidelines and protocols to run this loop has helped facilitate and improve blood glucose control, yet these available guidelines still leave the nurse with the overall responsibility for the safety of the patient with regard to glucose control. Therefore, one of the major hurdles for the safe implementation of tight glucose control is appropriate training and motivation of the nurses in an intensive care unit. With the objective to facilitate blood glucose control, nurses are faced with an additional responsibility for the patient. Nurses are developing a fear of running into hypoglycemic blood glucose ranges, they are not used to "dealing" with lower glucose concentrations, and also have, in general, not received special training on glucose control as, for example, well-controlled type 1 diabetic patients. In addition, when controlling glucose, several cofactors have an important impact in critically ill patients. These factors have a major impact on the actual insulin requirement, but are not considered by available titration protocols or guidelines. The severity of illness and/or the presence of infections is well known to have a major impact on the requirement of insulin/insulin sensitivity and caloric intake such as enteral or parenteral nutrition, but also the degree of gastric emptying or diarrhea has to be considered for appropriate insulin dosing. Another important factor that has a major effect on the amount of insulin required is concomitant medication such as corticosteroids or sympathicomimetics, which have a counterregulatory effect to insulin and can, in some cases, increase the insulin requirement dramatically.

Therefore, this question remains: *how can tight glucose control be safely established?* There are several options available in performing glucose control in the critically ill patient setting. The most straightforward approaches are highlighted in **Figure 2**.

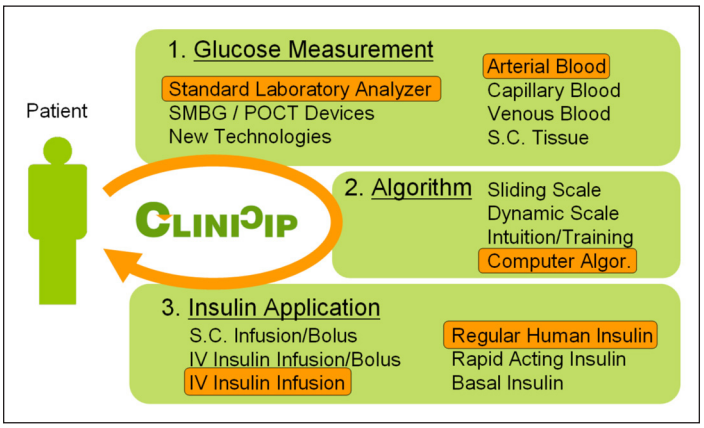

Figure 2. Options available in performing glucose control in the critically ill patient setting. Algor, algorithm; CLINICIP, closed loop insulin infusion for critically ill patients; IV, intravenous; POCT, point of care testing; S.C., subcutaneous; SMBG, self-monitoring of blood glucose.

The most standardized approach to measuring blood glucose is to draw arterial blood and use a standard laboratory analyzer for glucose measurement.[9] Although several "new technologies," e.g., continuous glucose sensors for the measurement of glucose in subcutaneous adipose tissue, have been developed, the reliability of this alternative measurement site in the critically ill patient setting to replace blood glucose measurements needs to be proven.[10,11]

With regard to the available guidelines, protocols, or algorithms to define the appropriate insulin dose, a fully automated computer algorithm (if available) that is capable of relieving nurses from their responsibility seems most appropriate.

Regarding the application of insulin, the intravenous infusion of regular human insulin has proven to be the best solution from the perspective of a fast regulatory response to the glucose reading, at least in the critically ill patient setting.

As for the patient in a general ward, the situation seems entirely different: (1) vascular access routes are much more difficult to establish and (2) the nurse-to-patient ratio is by far lower in a general ward, i.e., especially during nighttimes where there may be one single nurse responsible for up to 30 patients. Therefore, only a reliable automated system will allow controlling glucose levels to a desired level in this setting.

Conclusion

Tight glucose control is difficult to establish, both in critically ill patients and in patients in a general ward. Although there is clear evidence for an association between hyperglycemia and mortality in hospitalized patients, there is a lack of clinical intervention studies on the effect of glucose control in general wards. Thus, there is a clear need for the performance of randomized controlled outcome studies in this area, as well as reliable methods to control glucose homeostasis in this less than intensive care setting.

Disclosure:

Martin Ellmerer is a consultant for B. Braun AG and for Sensile Medical AG.

References:

1. Van den Berghe G, Wouters P, Weekers F, Verwaest C, Bruyninckx F, Schetz M, Vlasselaers D, Ferdinande P, Lauwers P, Bouillon R. Intensive insulin therapy in the critically ill patients. N Engl J Med. 2001;345(19):1359-67.
2. Van den Berghe G, Wilmer A, Hermans G, Meersseman W, Wouters PJ, Milants I, Van Wijngaerden E, Bobbaers H, Bouillon R. Intensive insulin therapy in the medical ICU. N Engl J Med. 2006;354(5):449-61.
3. Plank J, Blaha J, Cordingley J, Wilinska ME, Chassin LJ, Morgan C, Squire S, Haluzik M, Kremen J, Svacina S, Toller W, Plasnik A, Ellmerer M, Hovorka R, Pieber TR. Multicentric, randomized, controlled trial to evaluate blood glucose control by the model predictive control algorithm versus routine glucose management protocols in intensive care unit patients. Diabetes Care. 2006;29(2):271-6.
4. Pachler C, Plank J, Weinhandl H, Chassin L, Wilinska M, Kulnik R, Kaufmann P, Pilger E, Smolle K, Pieber TR, Ellmerer M, Hovorka R. Tight glycaemic control by an automated algorithm with time variant sampling in medical ICU patients. Intensive Care Med. In press 2008.
5. Umpierrez GE, Isaacs SD, Bazargan N, You X, Thaler LM, Kitabchi AE. Hyperglycemia: an independent marker of in-hospital mortality in patients with undiagnosed diabetes. J Clin Endocrinol Metab. 2002;87(3):978-82.
6. Standards of medical care in diabetes--2008. Diabetes Care. 2008;31 Suppl 1:S12-54.
7. Brunkhorst FM, Engel C, Bloos F, Meier-Hellmann A, Ragaller M, Weiler N, Moerer O, Gruendling M, Oppert M, Grond S, Olthoff D, Jaschinski U, John S, Rossaint R, Welte T, Schaefer M, Kern P, Kuhnt E, Kiehntopf M, Hartog C, Natanson C, Loeffler M, Reinhart K. Intensive insulin therapy and pentastarch resuscitation in severe sepsis. N Engl J Med. 2008;358(2):125-39.
8. Devos P, Preiser J, Melot C. Impact of tight glucose control by intensive insulin therapy on ICU mortality and the rate of hypoglycemia: Final results of the GLUCONTROL study [abstract]. Intensive Care Med. 2007;33 Suppl 2:189.
9. Kanji S, Buffie J, Hutton B, Bunting PS, Singh A, McDonald K, Fergusson D, McIntyre LA, Hebert PC. Reliability of point-of-care testing for glucose measurement in critically ill adults. Crit Care Med. 2005;33(12):2778-85.
10. Ellmerer M, Haluzik M, Blaha J, Kremen J, Svacina S, Toller W, Mader J, Schaupp L, Plank J, Pieber T. Clinical evaluation of alternative-site glucose measurements in patients after major cardiac surgery. Diabetes Care. 2006;29(6):1275-81.
11. Wentholt IM, Hoekstra JB, Devries JH. Continuous glucose monitors: the long-awaited watch dogs? Diabetes Technol Ther. 2007;9(5):399-409.