A liberal glycemic target in critically ill patients with poorly controlled diabetes?

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Due to severe physical stress, critically ill patients commonly develop hyperglycemia. Multiple observational studies have shown a U-shaped association between glycemic levels in the intensive care unit (ICU) and the risk of death, with the lowest risk of death associated with glucose levels that are normal for age (1-3). Three landmark randomized controlled trials (RCTs) performed in Leuven and several subsequent single-center studies found that treating pronounced hyperglycemia [>215 mg/dL (11.9 mmol/L)] with insulin to target age-adjusted normoglycemia [80–110 mg/dL (4.4–6.1 mmol/L) for adults, 60–100 mg/dL (3.9–5.6 mmol/L) for children, 50–80 mg/dL (2.8–4.4 mmol/L) for infants] reduced morbidity and mortality for both critically ill adults and children (4-8). Soon after these landmark RCTs, many ICUs worldwide adopted tight glycemic control (TGC) as part of their standard of care. Unfortunately, worldwide implementation of some degree of glycemic control impeded the design of a repeat multicenter RCT. Subsequent multicenter RCTs no longer compared TGC to severe hyperglycemia, but to an intermediate glycemic target, in general <180 mg/dL (10 mmol/L) (9-12). Compared to an intermediate target, these multicenter trials did not find an outcome benefit from targeting normoglycemia and the NICE-SUGAR study even found harm (9). Therefore, current guidelines recommend to target an intermediate level of glycemic control [<180 mg/dL (10 mmol/L)] in critically ill patients (13). However, there are no adequately powered RCTs that directly compared an intermediate versus a liberal glycemic target. In addition, apart from a different glycemic target in the control group, other methodological differences may account for the divergent results between Leuven and NICE-SUGAR. These include, among others, the use of inaccurate glucometers in NICE-SUGAR, the use of an unvalidated glucose control algorithm and a different feeding strategy (14,15). In the Leuven studies on TGC, patients received early parenteral nutrition in accordance with European feeding guidelines, an approach that was subsequently shown to be harmful (16). Therefore, the optimal glycemic target for critically ill patients remains to be defined, and this may differ according to the available logistics and the feeding strategy.

Another factor that may influence the efficacy of TGC is the patient population. In particular, some evidence suggests that patients with diabetes may benefit less or not from targeting normoglycemia, especially when glycemia was poorly controlled before ICU admission. Indeed, observational studies have shown that the U-shaped relationship between glycemia and mortality is at least flattened in the subgroup of diabetes patients, with the nadir in some studies at higher levels than in non-diabetic patients (1,2,17). Furthermore, observational data have suggested that the optimal glycemia may depend on the chronic level of glycemic control as deducted from the pre-admission HbA1c (18,19). Apart from this, chronic hyperglycemia induces adaptations, whereby acute lowering of glycemia may activate hypoglycemia-like responses already in the normoglycemic range (20). Altogether, this indirect evidence may suggest that critically ill patients with diabetes, especially those with poor glycemic control before ICU admission, may benefit from more liberal glycemic control in ICU.

In a recent article in Critical Care Medicine, Kar and colleagues published a prospective exploratory study on the effect of implementation of a liberal glycemic control

regimen in critically ill patients with poorly controlled type 2 diabetes (21). The objectives were to study whether it is safe to target higher glycemic levels and whether this decreases the rate of hypoglycemia. Briefly, adult critically ill patients with a HbA1c >7% upon admission and with a blood glucose level >180 mg/dL (10 mmol/L) were included. Type 1 diabetics were excluded. In the standard care period, glycemia was targeted at 108–180 mg/dL (6–10 mmol/L) as for non-diabetes patients, whereas in the 'liberal' period, 180–252 mg/dL (10–14 mmol/L) was targeted in the study group. Compared to the standard care period, there was a lower glycemic variability and a non-significant trend towards less hypoglycemic events. Biomarkers on inflammation and oxidative stress as well as clinical endpoints were similar. The authors concluded that targeting liberal glycemic control in critically ill patients with poorly controlled type 2 diabetes is safe and that further studies are justified to investigate whether this strategy is clinically superior.

Unfortunately, although the hypothesis and the results may appear plausible, several factors limit the internal and external validity of the findings.

First, the conclusion that targeting liberal glycemic control in the studied population is safe, is premature. Besides the fact that the study was observational and did not test a randomized intervention, the study was also clearly underpowered for clinical endpoints, with only 83 included patients. To cope with this, the authors measured biomarkers of inflammation and oxidative stress, in order to detect a signal of harm. As biomarkers were not significantly different, Kar *et al*. concluded that there was no harm. However, after day 2, biomarkers were obtained in less than 21 patients (<25% of the study population) and it is mainly after that time point that the achieved glycemic levels were slightly different. Hence, the study is inadequately powered to conclude that liberal glycemic control is safe in the study population.

Second, the achieved glycemic control was of suboptimal quality, as illustrated by the relatively high rate of severe hypoglycemia [≤40 mg/dL (2.2 mmol/L)] in the standard care group. In NICE-SUGAR, in a general ICU population, the rate of severe hypoglycemia was 0.5% with a similar glycemic target in the control group (9). Although the incidence of hypoglycemia is usually higher in diabetics than in non-diabetics, the incidence of severe hypoglycemia in the standard care group of the current study (9.8%) remains very high (21). Indeed, Egi *et al*. observed a much lower incidence in diabetes patients in a multicenter observational study with similar to even stricter glycemic targets (22). In this study, patients with poorly controlled diabetes (HbA1c ≥8%) had a rate of severe hypoglycemia of 4.3% and patients with a pre-admission HbA1c between 6.5% and 7.9% had a 2.5% rate of severe hypoglycemia. The high rate of hypoglycemia as well as the high glycemic variability in the current study could at least in part be explained by a poor glucose control algorithm. Indeed, the insulin infusion protocol was a strict if-then algorithm, with a fixed starting insulin infusion rate only depending on the actual glycemic value and independent of the patients' basal insulin needs and the feeding intake. Also the adaptations in insulin rate were fixed and the protocol included the use of (fixed) insulin boluses. By mainly considering the actual glycemic value and ignoring the trend and changes in food intake, the risk of hypoglycemia and of glycemic variability likely increased. The use of fixed insulin boluses may further have increased this risk. Besides that, per protocol, glycemia was more frequently controlled in the liberal period. The quality of glycemic control could have been improved by use of a glycemic control guideline that takes all above-mentioned factors into account and allows intuitive decision-making, as in the Leuven studies (4-6), or alternatively, by use of a validated computer algorithm. Our group has recently developed a reliable and validated glucose control computer algorithm, with a low rate of hypoglycemia and of glycemic variability (23). Recently, the efficacy and safety was confirmed in a multicenter RCT, with a similar performance of the algorithm in other centers (unpublished).

A third factor that limits internal and external validity of the current study is the presumed considerable overlap in glycemic management between both groups. HbA1c measurement, necessary before inclusion, was only performed once per week-day. Hence, patients admitted to the ICU in the evening or in the weekend could only be included on the next week-day and had standard care until that time. In addition, when insulin administration was switched from intravenous infusion to subcutaneous injection—a choice at the discretion of the attending physician—glucose targets were ceased. Insulin infusion tended to be stopped earlier in the standard care period, which could have inflated glycemic variability and have increased the rate of hypoglycemia, although the shorter insulin infusion could also be explained by a shorter length of stay in ICU (data not provided).

In contrast to the study of Kar *et al*., Furnary *et al*. found in a prospective observational study that targeting stricter levels of glycemia over years improved outcome in a large population of diabetes patients undergoing cardiac surgery (n=5,534) (24). The lowest mortality risk as well as lowest morbidity associated with achieved glycemic values <150 mg/dL (8.3 mmol/L). Interestingly, in this study HbA1c did not associate with outcome when corrected for other risk factors. Furthermore, in an observational before-after study, Krinsley found a benefit of implementing TGC in both diabetic and non-diabetic critically ill patients, although the benefit was less pronounced in diabetic patients. However, achieved glycemic levels above 180 mg/dL (10 mmol/L) clearly associated with a significantly higher risk of mortality also in diabetics (17).

Until now, no large RCT has specifically studied the population of (poorly controlled) diabetes patients. However, subgroup analyses of large multicenter RCTs did not find an opposite effect of the intervention in the diabetes population (9,11). In addition, a post hoc analysis of the adult Leuven studies on glycemic control showed that the subgroup of diabetes patients had no significant mortality benefit from TGC, but there was a trend towards reduced morbidity (25).

Hence, although there is a theoretical basis that critically ill patients with poorly controlled diabetes may benefit from more liberal glycemic control during ICU stay, evidence from RCTs is limited. In addition, even if the optimal glycemic target would be higher than in non-diabetics, there is insufficient evidence that the ideal target would be above 180 mg/dL (10 mmol/L). Due to the numerous methodological flaws, the current study only adds limited evidence to the field and the optimal glycemic target remains unclear, as is the case for non-diabetic critically ill patients.

In conclusion, landmark studies have shown that preventing severe hyperglycemia improves outcome of critically ill patients, but safe and effective implementation requires reliable monitoring tools and experience. Glycemic control can be optimized by a validated glucose control computer algorithm, which limits the risk of hypoglycemia and glycemic variability. The optimal glycemic target for critically ill patients remains unclear and may differ according to the available logistics, the used feeding regimen and the diabetes status. Whether the optimal glycemic level in critically ill patients should be determined individually based on the premorbid HbA1c is the scope of a currently recruiting RCT (26). While awaiting new RCTs, common sense supports to avoid severe hyperglycemia in all ICU patients.

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Footnote

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