

## VIEWPOINT

# Intensive insulin therapy to control hyperglycemia in the critically ill: a look back at the evidence shapes the challenges ahead

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### Abstract

The major interventional trials of intensive insulin therapy in critically ill patients have reached divergent results. The present viewpoint article explores some of the potential reasons, including differences in monitoring technology and protocol design and performance, the occurrence of severe hypoglycemia and changes in the standard of care since publication of the landmark single-center trial. Recently published data detailing the deleterious effect of hypoglycemia are discussed, as is the emerging body of literature describing the important impact of glycemic variability on the risk of mortality in heterogeneous populations of acutely ill and severely ill patients. These new findings have important implications for the design of future interventional trials of intensive insulin therapy in the intensive care unit setting.

The story of glucose control has been one of the most passionate discussions in critical care medicine for nearly an entire decade, since publication of the landmark single-center trial of intensive insulin therapy targeting euglycemia in a cohort of mechanically ventilated surgical intensive care unit (ICU) patients [1]. A subsequent trial from the same institution involving medical ICU patients did not yield such strikingly positive results [2], and additional randomized trials have suggested no benefit from this intervention [3-7] or even a modest signal of harm [8]. Nonrandomized trials [9-11] and a large body of observational cohort data from heterogeneous populations [12-14] suggest strongly that a J-shaped or U-shaped mortality curve exists among acutely and

critically ill patients, with the lowest mortality occurring among those patients with mean glucose levels during their ICU stay in the range 90 to 120 mg/dl and higher rates of mortality for those patients with levels below or above this range.

How does one reconcile these seemingly divergent findings? Clearly, based on the rules of evidence-based medicine, recommendations and guidelines [15,16] cannot presently support a widespread implementation of insulin protocols targeting euglycemia; a more conservative and safe effective glucose control approach has been suggested [17] and probably reflects the current practice in many ICUs.

Glycemic control is considerably more complex than most interventions in critical care medicine, helping to explain variances in outcomes of the clinical trials. Very recently, Schultz and collaborators thoroughly reviewed the possible causes of discrepancies between the pioneering trial and the subsequent studies [18]. Monitoring issues include the use of different sources of blood (arterial, venous, capillary) measured using a variety of different monitoring technologies (central laboratory analyzer, portable arterial blood gas analyzer, bedside glucometer) with widely divergent degrees of accuracy [19-21]. Moreover, these measurements are frequently performed in unstable patients with dynamic degrees of insulin resistance and risk of hypoglycemia [22]. Each cycle of measurement and potential modification of therapy is time consuming, and must be repeated every 1 to 4 hours throughout the patient's stay in the ICU [23].

The skill, motivation and experience of the treatment team can influence the protocol performance and a trial's results; these factors may help explain the more positive results emanating from single-center trials. There were 758 and 600 patients in the treatment arm of the two Leuven trials [1,2], and 800 patients in the interventional arm of the before-and-after Stamford trial [9], notable for its positive results and an absence of an increase in severe hypoglycemia (SH), confirmed in several large cohort studies as being independently associated with increased risk of mortality [24-27]. In contrast, there were means of

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only 15 and 26 patients per institution in the interventional arms of the GLUCONTROL trial [3] and the VISEP trial [4]. Skill with protocol performance and the chosen monitoring technology (portable laboratory analyzer vs. bedside glucometer) probably impacted not only the rates of SH, but also the degree to which the interventional cohorts achieved their targeted glycemic range.

Chase and colleagues reported recently in *Critical Care* that glycemic control using a highly performing algorithm for glycemic control resolved organ failure faster, and for a greater percentage of patients with similar admission and maximum Sequential Organ Failure Assessment scores, than the retrospective conventional control [28]. Moreover, errors in insulin administration are the commonest therapeutic mistakes in ICUs [29]. The change in the standard of care over time that resulted in the control arm of the most recent multicenter trial [8] having a glycemic target range much lower than that used in the first Leuven trial [1] produced a lower degree of glycemic separation between the interventional and conventional cohorts, magnifying the importance of the deleterious effect of hypoglycemia. The commonplace use of insulin for treatment of moderate hyperglycemia has therefore significantly increased the size of a trial that would be adequately powered to potentially demonstrate benefit of the intervention.

An understanding of these factors and a review of emerging themes relating to the dysglycemia of critical illness lays the groundwork for the design and creation of the sorts of interventional trials that will best define the role of glycemic interventional trials in the critically ill patient. While previous trials have focused on control of overall blood glucose (BG) levels, using specific BG targets for the control and interventional arms, recent literature has introduced and reinforced the principle that future trials cannot ignore two other domains of glycemic control: hypoglycemia and glycemic variability (GV).

Although the authors of the Leuven 1 study reported that SH – defined as BG <40 mg/dl – that occurred in 5.1% of the patients in the interventional arm [1] did not adversely affect outcomes, subsequent analysis of these data, as well as the results of several large observational cohort studies, suggested otherwise [30]. A retrospective analysis of a cohort of 5,365 patients admitted to a single medical–surgical ICU demonstrated that the odds ratio (OR) for mortality associated with a single episode of SH was 2.28 (95% confidence interval (CI) = 1.41 to 3.70,  $P = 0.008$ ) [25]. Moreover, a 1:3 nested case:control analysis of 102 patients with SH from this investigation matched to patients without SH by age, diagnostic category, diabetic status, treatment era and severity of illness confirmed significantly higher mortality in the patients who experienced SH (55.9% vs. 39.5%,  $P = 0.0057$ ).

Similarly, Bagshaw and colleagues evaluated the highest and lowest glucose values among 66,184 Australian patients from a mix of 24 ICUs and found that a single episode of SH was independently associated on multivariable analysis with increased risk of mortality (OR = 2.6; 95% CI = 2.1 to 3.2) [26]. Egi and coworkers recently published a more in-depth analysis of 4,946 patients from two of these 24 ICUs, and found that even mild degrees of hypoglycemia independently confirmed increased risk of mortality as well as infection. Specifically, the ORs for mortality among groups of patients with varying levels of minimum BG, compared with those patients with nadir BG of 72 to 81 mg/dl, were as follows: 54 to 63 mg/dl, OR = 1.93 (95% CI = 1.27 to 2.95,  $P = 0.002$ ); 45 to 54 mg/dl, OR = 2.13 (95% CI = 1.29 to 3.53,  $P = 0.003$ ); 36 to 45 mg/dl, OR = 2.14 (95% CI = 1.20 to 3.81,  $P = 0.01$ ); and <36 mg/dl, OR = 2.99 (95% CI = 1.67 to 5.37,  $P < 0.001$ ) [27]. Pooled results from the two Leuven studies similarly provide support for the concept that SH is deleterious in critically ill patients [30]. The OR for mortality among 2,758 medical and surgical ICU patients was 3.23 (95% CI = 2.25 to 4.64,  $P < 0.0001$ ).

Finally, hypoglycemia is correlated with severity of illness in some studies [25] but not all [30]. While multivariable logistic regression modeling cannot completely exclude the problem of residual confounding, this type of analysis will be the strongest level of evidence available to clinicians; there will never be a randomized, controlled trial of induced hypoglycemia or deliberately increased GV in a cohort of critically ill patients.

There are two clear implications from these studies. First, there can be no doubt that the outcomes of the major interventional trials on intensive insulin therapy in various critically ill populations were significantly affected by the high rates of SH that occurred among patients in their interventional arms, ranging from 6.8% of the patients in the NICE-SUGAR trial [8] to 18.7% in the Leuven medical ICU trial (25.0% of those in the ICU for 5 days or more) [2]. Second, future glycemic management interventions must be designed to minimize the occurrence not only of SH, but also of mild to moderate hypoglycemia.

While GV was not on any investigator's radar screen during design, implementation or publication of the interventional trials of glycemic control in the critically ill, new literature has identified GV as an aspect of glycemic control that may have an even larger bearing on outcomes than does reduction of overall glycemic levels. A retrospective analysis of a cohort of 3,252 patients admitted to a mixed medical–surgical ICU found that those patients in the lowest quartile of GV – based on the standard deviation of the mean glucose level – had an OR for mortality of 0.49 (95% CI = 0.38 to 0.63,  $P < 0.0001$ ), while those in the highest quartile of GV sustained an

increased risk of mortality (OR = 1.81, 95% CI = 1.47 to 2.22) [31]. Indeed, among patients with a mean glucose level of 70 to 99 mg/dl during their ICU stay – at first glance, the patients with the best glycemic control – the mortality ranged from 5.9 to 30.1% compared with those patients with the lowest and highest variability.

Additional work from this institution demonstrated that the deleterious effect of increased GV was seen only among nondiabetic patients [32], in concordance with a stream of literature suggesting that hyperglycemia in critically ill patients has a much greater adverse effect among nondiabetics than among diabetics [33-35]. Other retrospective investigations among a variety of different patient populations have confirmed that increased GV is independently associated with increased risk of mortality [36-39].

Finally, the Leuven investigators recently published the first analysis of the effect of GV in a prospective randomized controlled trial [30]. This important investigation confirmed that increased GV was independently associated with increased risk of mortality, both in the medical ICU and the surgical ICU studies. Moreover, the intervention – intensive insulin therapy – failed to reduce GV, and in fact tended to increase GV in both cohorts. Failure to improve GV may therefore have diminished the beneficial effects of the intervention, providing support for the inclusion of this domain of glycemic control as a secondary endpoint in future interventional trials [40].

The importance of these observations is strengthened by their biologic plausibility. Indeed, *in vitro*, a high glucose variability can induce apoptosis of endothelial cells and impairment of the cellular signaling in monocytes [41,42]. These effects may be mediated via wide changes in osmolarity that in turn could affect cellular and organ function [43]. Previous investigations in diabetics have suggested that serum markers of endothelial dysfunction and oxidative stress are increased in those patients who experience glucose fluctuation independent of the average glucose exposure [44]. Harm to the microvasculature mirrored by the elevation of markers of endothelial dysfunction could hence be further accelerated by hyperactive inflammatory cells. Finally, although the most speculative, perhaps the most important reason why increased GV may be associated with worsened ICU outcomes is the fact that significant hypoglycemia could occur undetected. Because continuous glucose monitoring has not yet been widely used in ICU patients, no active surveillance program can eliminate the possibility that significant glucose swings are occurring.

Future interventional trials of insulin therapy in critically ill patients must therefore control all three domains of BG control: lowering overall glycemic levels, while minimizing both GV and hypoglycemia. There are

several approaches that may, in combination, help ICU teams achieve the best possible outcomes [45]. One such approach is the use of computerized algorithms to improve work flow, increase adherence to glycemic targets and minimize errors in insulin dosing, resulting in decreased rates of hypoglycemia. In fact, a large multicenter French trial – Computerized Glucose Control in Critically Ill Patients (CGAO-Rea, Clinicaltrials.gov NCT01002482) – is currently underway to compare the outcome of patients randomized to computer-guided glucose control versus usual care [46]. Additionally, substantial improvements in glycemic protocol performance and decreases in the time burden of the intervention are likely to accrue from the use of accurate continuous or near-continuous glucose monitoring technologies [47,48].

The increased frequency of monitoring resulting from the use of these new monitors should eliminate the occurrence of SH, and should markedly reduce the occurrence of mild to moderate hypoglycemia since the nursing staff attending the patient will have adequate warning to correct the trajectory of BG values before they reach dangerous levels. Moreover, continuous or near-continuous monitoring technology will provide clinicians with a tool to minimize GV, especially with the integration of insulin and nutrition delivery into the treatment algorithms.

In conclusion, glucose can no longer be considered an innocent bystander in the ICU; both hyperglycemia and hypoglycemia harm our patients. The lessons we have learned from the interventional trials performed over the past 9 years and the compelling evidence from recent investigations regarding the impact of hypoglycemia and GV lay the groundwork for the design and implementation of the next generation of trials. While many unanswered questions remain, there can be consensus that the literature has moved past the paradigm of a pro-con debate and towards a deeper appreciation of the importance of glycemic control in the critically ill patient and the challenges that clinicians still face.

#### Abbreviations

BG, blood glucose; CI, confidence interval; GV, glycemic variability; ICU, intensive care unit; OR, odds ratio; SH, severe hypoglycemia.

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