EDITORIAL

The goal of personalized glucose control in the critically ill remains elusive

James S. Krinsley^{1*} , Adam M. Deane² and Jan Gunst³

© 2021 Springer-Verlag GmbH Germany, part of Springer Nature

Twenty years after the landmark randomized controlled trial (RCT) reporting reduced morbidity and mortality with tight glucose control in the intensive care unit (ICU) [1], the ideal blood glucose (BG) target for critically ill patients remains debated. Indeed, although subsequent single-center RCTs confirmed benefit [2, 3], multicenter RCTs were largely neutral [4], and the NICE-SUGAR RCT [5] demonstrated increased mortality with tight glucose control, which the investigators attributed to an increased incidence of moderate and severe hypoglycemia [6]. Although these opposing results may be explained by numerous factors including differences in BG target, accuracy of BG measurements, and feeding strategies, emerging evidence from observational and sequential-period studies suggests that the ideal BG target may depend on the pre-existing level of glucose control as reflected by glycated haemoglobin (HbA1c) at ICU admission, whereby patients with ‘inadequately controlled’ diabetes may benefit from maintaining BG at greater concentrations than those that are optimal or normal for critically ill patients with no or ‘well-controlled’ diabetes [7–10]. Sustained hyperglycemia may decrease expression and function of GLUT1 and GLUT4 transporters [11], potentially increasing vulnerability to absolute, or even relative hypoglycemia, i.e. excursions into glucose ranges >30% below the estimated chronic BG level [12]. These data provide a pathophysiological basis for the implementation of ‘individualized’ or ‘personalized’ glucose control strategies based on the degree of preadmission glycemic control.

The CONTROLLING RCT [13], published in this issue of Intensive Care Medicine, investigated the impact of an individualized glucose control strategy as compared to conventional glucose control. The authors are to be warmly congratulated for conducting an RCT of such a complex intervention that attempts to answer a clinically important question. In addition to the multi-center randomized design, the methodology is notable for the attempt to blind clinicians to the study intervention, as all previous large RCTs have been open-label. Finally, the investigators reported a rich set of clinical and glucose control metrics.

A total of 2075 patients were randomized, of whom 1917 received the intervention. Randomization occurred (median) 1.2 days after ICU admission with at least 25% of patients randomized after ≥ 2.1 days in ICU. Whilst this time period reflects the challenges of conducting such a trial, with delays occurring as part of screening and awaiting HbA1c determination, this introduces contamination bias. Indeed, in the interventional arm, patients were exposed to conventional glucose control (the comparator) for a median (IQR) of 26% (11–45%) of time in ICU.

In the individualized arm, BG target was based on the HbA1c-derived mean preadmission glycemia plus or minus 15 mg/dL (0.8 mmol/L). The BG target in the control arm was 151–180 mg/dL (8.4–10 mmol/L) for patients requiring insulin to reach concentrations below 180 mg/dL (10.0 mmol/L). For both groups, glucose control was managed using a non-commercial web-based application (<https://cpg.chu-lyon.fr>), with an algorithm based on multiple insulin-infusion sliding scales and rules to move within and between scales, taking the previous BG and nutritional changes into account.

Glucose control in critically ill patients is a dynamic process requiring frequent insulin titrations to achieve a BG target. The algorithm used in the CONTROLLING

*Correspondence: jkrinsley@stamhealth.org; james.krinsley@gmail.com

¹ Division of Critical Care, Department of Medicine, Stamford Hospital and Columbia Vagelos College of Physicians and Surgeons, Stamford, CT, USA

Full author information is available at the end of the article

study was not validated to guide individualized treatment prior to trial conduct. Moreover, blinding of all but last glucose values may have precluded the possibility to overrule the algorithm. Protocol performance assumes great importance in interpreting the trial results. More BG measurements were done in the intervention group (median (IQR) 7 (5–9) vs. 5 (3–8), $p < 0.0001$). While the time in the individualized target range was modest (51% [35–69%]), this reflects the challenge of conducting trials of a complex intervention over a large number of sites. Severe hypoglycemia (< 40 mg/dL [< 2.2 mmol/L]) was not statistically different between group (3.9% vs. 2.5%, $p = 0.09$) but hypoglycemia (defined in this study as BG < 72 mg/dL [< 4 mmol/L]) was more frequent with the intervention (31.2% vs. 15.8%, $p < 0.0001$). Notably, in cases of severe insulin resistance, the algorithm dictated to continue relatively large insulin doses unless BG decreased below 63 mg/dL [3.5 mmol/L], a level independently associated with mortality in several interventional and observational studies [7, 9, 14]. Also in the CONTROLLING study, moderate and severe hypoglycemia were associated with significantly increased mortality. While harm of short-lasting hypoglycemia may be context-dependent [9, 15], prolonged, recurrent or severe hypoglycemia should be prevented. It should therefore be recognized that the protocol used in this trial recommended to repeat BG one hour after a hypoglycemia episode, which may not prevent prolonged hypoglycemia.

The study was stopped prematurely by the data safety monitoring board due to a low likelihood of benefit and the potential harm associated with hypoglycemia. The primary outcome, 90-day mortality, was not different (308/938 [32.8%] in the intervention group vs. 295/968 [30.5%] in the control group, $p = 0.2$). Notably, time-weighted mean BG (reported in 1828 patients) differed by only 13 mg/dL (0.7 mmol/L). In 335 patients, the mean difference was 20–26 mg/dL (1.1–1.4 mmol/L), a finding that is statistically and, possibly, clinically significant. Among the remaining 1493 patients (82% of the entire cohort), the mean difference ranged from 0 to 11 mg/dL (0–0.6 mmol/L), which cannot be considered clinically significant. In contrast, the first Leuven RCT resulted in a 50 mg/dL (2.8 mmol/L) difference in mean morning BG between study groups [1]. Unfortunately, the CONTROLLING investigators did not anticipate a much smaller between-group BG difference, and calculated sample size on even a greater mortality benefit than observed in the first Leuven RCT. Therefore, the trial is underpowered to identify mortality differences with individualized glucose control.

What lessons can the critical care community draw from the CONTROLLING study? First, the association of hypoglycemia with mortality is reconfirmed. Second,

future RCTs should ensure adequate sample sizes for the primary outcome and sufficient treatment separation to identify differences in outcomes if one exists. Finally, despite the great efforts of the CONTROLLING investigators and the important data provided, the crucial question—whether BG management should be “personalized” based on preadmission glycemia or not—remains unanswered two decades after publication of the RCT that initiated such intense interest in the management of hyperglycemia in the critically ill.

Author details

¹ Division of Critical Care, Department of Medicine, Stamford Hospital and Columbia Vagelos College of Physicians and Surgeons, Stamford, CT, USA. ² Department of Critical Care, The University of Melbourne, Melbourne Medical School, Parkville, VIC, Australia. ³ Department of Cellular and Molecular Medicine, Clinical Division and Laboratory of Intensive Care Medicine, KU Leuven, Leuven, Belgium.

Declarations

Conflicts of interest

The authors declare that they have no conflicts of interest.

Publisher's Note

Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

Received: 2 September 2021 Accepted: 5 September 2021

Published online: 17 September 2021

References

1. Van den Berghe G, Wouters P, Weekers F et al (2001) Intensive insulin therapy in critically ill patients. *N Engl J Med* 345:1359–1367
2. Van den Berghe G, Wilmer A, Hermans G et al (2006) Intensive insulin therapy in the medical ICU. *N Engl J Med* 354:449–461
3. Vlasselaers D, Milants I, Desmet L et al (2009) Intensive insulin therapy in paediatric intensive care: a prospective, randomised controlled study. *Lancet* 373:547–556
4. Preiser JC, Devos P, Ruiz-Santana S et al (2009) A prospective randomised multi-centre controlled trial on tight glucose control by intensive insulin therapy in adult intensive care units: the Glucontrol study. *Int Care Med* 35:1738–1748
5. NICE-SUGAR Study Investigators (2009) Intensive versus conventional glucose control in critically ill patients. *N Engl J Med* 360:1283–1297
6. The NICE-SUGAR Study Investigators (2012) Hypoglycemia and risk of death in critically ill patients. *N Engl J Med* 367:1108–1118
7. Egi M, Bellomo R, Stachowski E et al (2011) The interaction of chronic and acute glycemia with mortality in critically ill patients with diabetes. *Crit Care Med* 39:105–111
8. Krinsley JS, Preiser JC, Hirsch IB (2017) Safety and efficacy of personalized glycemic control in critically ill patients: a 2 year before and after interventional trial. *Endo Prac* 23:318–330
9. Krinsley JS, Rule P, Pappy L et al (2020) The interaction of acute and chronic glycemia on the relationship of hyperglycemia, hypoglycemia and glucose variability to mortality in the critically ill. *Crit Care Med* 48:1744–1751
10. Luethi N, Cioccarl L, Biesenbach P et al (2018) Liberal glucose control in ICU patients with diabetes: a before-and-after study. *Crit Care Med* 46:935–942
11. Stringer DM, Zahradka P, Taylor CG (2015) Glucose transporters: cellular links to hyperglycemia in insulin resistance and diabetes. *Nutr Rev* 73:140–154

-
12. Kwan TM, Zwakman-Hessels L, Marhoon N et al (2020) Relative hypoglycemia in diabetic patients with critical illness. *Crit Care Med* 48:e233–e240
 13. Bohé J, Abidi H, Brunot V et al (2021) Individualised versus conventional glucose control in critically-ill patients The CONTROLLING Study. A randomized clinical trial. *Intensive Care Med*. <https://doi.org/10.1007/s00134-021-06530-y>
 14. Krinsley JS, Egi M, Kiss A et al (2013) Diabetic status and the relationship of the 3 domains of glycemic control to mortality in critically ill patients: an international multi-center cohort study. *Crit Care* 17:R37
 15. Mesotten D, Gielen M, Sterken C et al (2012) Neurocognitive development of children 4 years after critical illness and treatment with tight glucose control: a randomized controlled trial. *JAMA* 308:1641–1650