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Does the achievement of an intermediate glycemic target reduce organ failure and mortality? A post hoc analysis of the Glucontrol trial☆,☆☆,★

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ABSTRACT

Objective: This research evaluates the impact of the achievement of an intermediate target glycemic band on the severity of organ failure and mortality.
Methods: Daily Sequential Organ Failure Assessment (SOFA) score and the cumulative time in a 4.0 to 7.0 mmol/L band (*c*TIB) were evaluated daily up to 14 days in 704 participants of the multicentre Glucontrol trial (16 centers) that randomized patients to intensive group A (blood glucose [BG] target: 4.4-6.1 mmol/L) or conventional group B (BG target: 7.8-10.0 mmol/L). Sequential Organ Failure Assessment evolution was measured by percentage of patients with SOFA less than or equal to 5 on each day, percentage of individual organ failures, and percentage of organ failure–free days. Conditional and joint probability analysis of SOFA and cTIB 0.5 or more assessed the impact of achieving 4.0 to 7.0 mmol/L target glycemic range on organ failure. Odds ratios (OR) compare the odds risk of death for *c*TIB 0.5 or more vs *c*TIB less than 0.5, where a ratio greater than 1.0 indicates an improvement for achieving *c*TIB 0.5 or more independent of SOFA or glycemic target.
Results: Groups A and B were matched for demographic and severity of illness data. Blood glucose differed between groups A and B ($P < .05$), as expected. There was no difference in the percentage of patients with SOFA less than or equal to 5, individual organ failures, and organ failure–free days between groups A and B over days 1 to 14. However, 20% to 30% of group A patients failed to achieve *c*TIB 0.5 or more for all days, and significant crossover confounds interpretation. Mortality OR was greater than 1.0 for patients with cTIB 0.5 or more in both groups but much higher for group A on all days.
Conclusions: There was no difference in organ failure in the Glucontrol study based on intention to treat to different glycemic targets. Actual outcomes and significant crossover indicate that this result may not be due to the difference in target or treatment. Odds ratios–associated achieving an intermediate 4.0 to 7.0 mmol/L range improved outcome.

1. Introduction

Rate, severity, and lack of resolution of organ failure are strongly associated with increased morbidity and mortality in intensive care unit (ICU) patients [1]. Organ failure is typically assessed daily by the Sequential Organ Failure Assessment (SOFA) score [2-4]. Van den Berghe et al [5] suggested that glucose control could improve organ failure, and, recently, cumulative time in an intermediate glycemic band (4.0-7.0 mmol/L) (*c*TIB) was associated with improved rate and severity of organ failure, based on a different study [6]. However, glycemic control and targets are contentious [7,8]. Although decreased mortality was found in some studies [5,6,9], others did not [10-12], and many saw no difference [13-15]. Therefore, moderate targets are currently recommended [16,17], despite evidence that intermediate target ranges could favorably influence organ failure rate and severity.

☆ Competing interests: The authors declare that they have no competing interests.
☆☆ Authors' contribution: JCP and CM conducted the trial and made the acquisition of data during the Glucontrol study. All authors were involved in the analysis and interpretation of data. The manuscript was originally drafted by SP, JGC, and JCP, but all authors made contributions through the entire process, including reading and final approval of this manuscript.
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This study evaluates the impact and interaction of organ failure and glycemic control in the Glucontrol trial [10] that compared separate glycemic target bands, one of which is entirely within the 4.0 to 7.0 mmol/L band used by Chase et al [18], whereas the others did not overlap. This randomized trial data provide a further opportunity to examine the interaction of glycemic level and organ failure and how initial results [18] generalize over an independent cohort.

2. Methods

2.1. Glucontrol

Glucontrol was a prospective, randomized, multicenter controlled glucose control trial implemented in 19 centers (21 ICUs) from November 2004 to May 2006 [10]. The 1078 patients were randomized to group A (target: 4.4-6.1 mmol/L) or group B (target: 7.8-10.0 mmol/L). Insulin infusion dosing was defined using sliding scales, with blood glucose (BG) measured hourly when not in the target range. For limited variation (≤50%) of BG levels, 2 hourly and 4 hourly measurements were allowed. Details are in [10].

2.2. Organ failure

Daily SOFA score was used [2,19], calculated based on 5 of the 6 individual scores of 1 to 4. The Glasgow Coma score is excluded due to its reported lack of robustness and unreliability [18]. Thus, total SOFA score ranges from 0 to 20. All SOFA scores were recalculated from original clinical data to avoid bias. A total SOFA less than or equal to 5 is used as a threshold to discriminate patients considered relatively well and more likely to recover.

2.3. Glycemic outcome

Glycemic outcome and quality of control are measured by cTIB for the first 14 days of stay. It was calculated per day and per patient and is defined as the percentage of time the patient's BG levels have been cumulatively in a specific band (4.0-7.0 mmol/L here) up to and including the considered day. This band includes the entire group A target range and none of the group B target range. All other glycemic results are presented for clarity, including per-patient cTIB values to measure differences in control achieved vs intended between groups A and B and the moderate (BG < 4.0 mmol/L) and severe (BG < 2.2 mmol/L) hypoglycemic events.

2.4. Patients and data

Sequential Organ Failure Assessment data measurement varied between centers, and patients were only included, where sufficient SOFA data were available (Fig. 1). All data from centers with more than 40% missing data were excluded. Per-center exclusion allows the remaining patients to be still representative of ICU population and properly randomized. In addition, patients for whom interpolation of missing data from surrounding data cannot be performed were also removed, as detailed in Fig. 1. Overall, 374 of 1078 patients were excluded, and the remaining 704 patients are summarized in Table 1 by patient group. Both groups were similar for age, sex, diagnostic category, and Acute Physiology And Chronic Health Evaluation (APACHE) II score. Ethical consent was obtained from ethics committee of each participating hospital, and included patients have signed consent allowing the audit, analysis, and publication of these data.

2.5. Analyses and statistical methods

For each patient, daily SOFA score and cTIB are calculated. Sequential Organ Failure Assessment score improvement is measured by the evolution of the percentage of patients with SOFA less than or equal to 5 dividing patients into SOFA less than or equal to or SOFA more than 5. Proportions of SOFA less than or equal to 5 are compared for each day using a Fisher exact 2-sided test, where $P < .05$ is considered significant.

Patients are also characterized in each group by quality of control and glycemic outcome (cTIB ≥ 0.5 or cTIB < 0.5). Conditional (Probability (P) [SOFA ≤ 5 | cTIB ≥ 0.5]) and joint probabilities (defined in Table 2) assess the link between organ failure and glycemic outcome.

To assess the impact of control quality (cTIB) independent of organ failure, the odds ratio (OR) for each group is calculated comparing the odds risk of death for cTIB 0.5 or more vs cTIB less than 0.5 on each day, where a ratio greater than 1.0 indicates an improvement for achieving cTIB 0.5 or more independent of SOFA score results.

Organ failure–free days (OFFD) are defined by the number of days (percentage of total) a patient has no SOFA score component greater than 2. Organ failure–free days is a surrogate for the speed of resolution and/or prevention of organ failure [18]. Individual organ (component) failures (IOF) is the percentage of individual SOFA score components equal to 3 or 4 from the maximum possible IOF (maximum, 5 components × total patient days of ICU stay) and is a measure of cohort organ failure. Individual organ failures and OFFD are compared between groups A and B using a 2-sided Fisher exact test.

3. Results

Table 3 shows initial and maximum SOFA score, and initial BG is equivalent over groups ($P \geq .4$). Group A has lower BG levels than patients from group B ($P < .05$), more hypoglycemia, and greater per-patient cTIB, as in Chase et al [18] and thus as expected.

Fig. 2 shows SOFA improves slightly for both groups over the first 12 to 14 days. Table 4 shows patient numbers per day in each group in

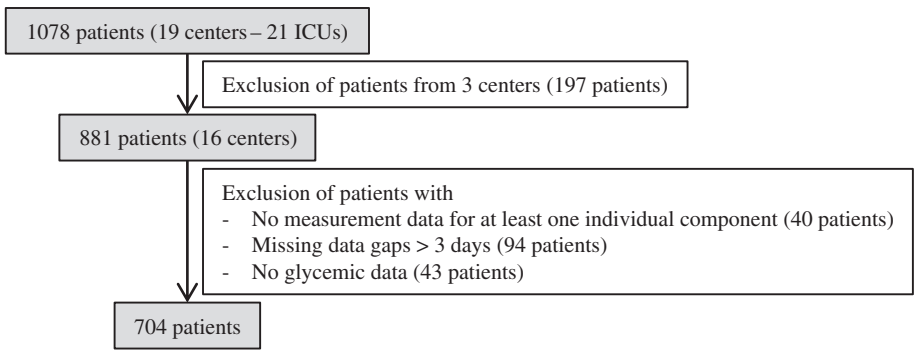

Fig. 1. Patient selection details.