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Glucose control positively influences patient outcome: A retrospective study

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ABSTRACT

Objective: The goal of this research is to demonstrate that well-regulated glycemia is beneficial to patient outcome, regardless of how it is achieved.
Methods: This analysis used data from 1701 patients from 2, independent studies. Glycemic outcome was measured using cumulative time in band (cTIB), calculated for 3 glycemic bands and for threshold values of $t = 0.5$, 0.6, 0.7, and 0.8. For each day of intensive care unit stay, patients were classified by cTIB, threshold, and hospital mortality, and odds of living (OL) and odds ratio were calculated.
Results: The OL given cTIB $\geq t$ is higher than the OL given cTIB $< t$ for all values of t, every day, for all 3 glycemic bands studied. The difference between the odds clearly increased over intensive care unit stay for $t > 0.6$. Higher cTIB thresholds resulted in larger increases to odds ratio over time and were particularly significant for the 4.0 to 7.0 mmol/L glycemic band.
Conclusion: Increased cTIB was associated with higher OL. These results suggest that effective glycemic control positively influences patient outcome, regardless of how the glycemic regulation is achieved. Blood glucose < 7.0 mmol/L is associated with a measurable increase in the odds of survival, if hypoglycemia is avoided.

1. Introduction

High and variable blood glucose (BG) levels have been associated with increased mortality in critically ill patients [1–5]. Glycemic control (GC) has significantly reduced mortality [6–8], but many studies have failed to reproduce these results [9–12]. These contradictory results have engendered skepticism toward GC in the critically ill patients [13–16].

There are 3 main difficulties with GC. First is a high risk of hypoglycemia [4,17–19], which is independently associated with poor outcome [4,19], where only one study reduced hypoglycemia during GC [8]. Second, all GC protocols specify a limit or target band with the aim of reducing persistent hyperglycemia, to best ensure improved patient outcome. However, there is currently no expert consensus about a best GC target band [13,20,21]. Third, metrics of performance for GC can typically only be evaluated at the end of the patient stay in the intensive care unit (ICU) [22]. However, it is important that clinicians are able to assess GC performance with respect to potential outcome at any time during stay to inform clinical decision making.

The goal of this research is to demonstrate that well-regulated glycemia is beneficial to patient outcome, regardless of how it is achieved. Key to this demonstration is a metric that continuously and adequately captures the concept of "well regulated." We strongly agree with MacKenzie et al [23] that both glycemic level and variability are essential components of well-regulated glycemia. Cumulative time in band (cTIB) is a simple metric that fulfills these criteria and enables us to investigate the impact of glycemia on patient outcome in terms of total exposure to predefined glycemic bands. Thus, we reanalyze data from 2 different GC trials and use an odds ratio (OR) based on cTIB and mortality to show that certain glycemic bands are better than others.

2. Subjects and methods

2.1. Patients

This study used glycemic data from 1701 patients from 2 independent studies:

Abbreviations: BG, blood glucose; CI, confidence interval; cTIB, cumulative time in band; GC, glycemic control; ICU, intensive care unit; OL, odds of living; OR, odds ratio.

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1. SPRINT: prospective SPRINT and retrospective pre-SPRINT cohorts were included in this study. These patients were admitted to Christchurch Hospital ICU between January 2003 and May 2007 (N = 784) [8,24].
2. Glucontrol: a randomized multicenter study, admitted to ICUs from 3rd November 2004 to 30th May 2006 (N = 917) [9].

These 2 data sets represent very different ICU cohorts with conflicting results in GC trials. SPRINT reduced organ failure, mortality, and hypoglycemia compared with the retrospective cohort [8,24]. The Glucontrol trial showed no benefit from GC to a low target compared with a higher target and, as is often the case, reported increased hypoglycemia for the low target cohort [9]. Patient data are summarized in Table, and the number of patients remaining in the ICU at each day is shown in Fig. 1.

2.2. Analysis

Glycemic outcome and performance were measured using cTIB, calculated for each patient for each day of stay. Cumulative time in band is the time spent within the predefined glycemic band as a proportion of the total time up to and including the day under consideration [24]. Furthermore, each patient day was classified into a category based on whether their cTIB value exceeded a predefined threshold, t, permitting a simple analysis of cohort behavior. Thus, for a given threshold, t, cTIB accounts simultaneously for both BG level and variability, where variability within the band is tolerated and more time (higher t) within a band of defined width limits overall variability.

To enable comparison, cTIB must be calculated from data with a constant measurement frequency. Clinical measurements from these retrospective data were not necessarily hourly; thus, interpolated data were used in the calculation of cTIB when required. Across the entire cohort, the average duration between measurements was 2.5 hours. The analyses were performed for the first 14 days of glycemic monitoring, which typically commenced shortly after admission to the ICU. After 14 days, less that 15% of patients remained in the ICU.

In this study, cTIB was calculated for the 4.0 to 7.0, 5.0 to 8.0, and 4.0 to 8.0 mmol/L glycemic bands. These bands represent 2 different intermediate glycemic levels with similar tolerated variability (4.0-7.0 and 5.0-8.0 mmol/L) and a wider band allowing more variability (4.0-8.0 mmol/L). These specific ranges were considered because they could reasonably be used as target bands for GC given current thinking [2,25–27]. Threshold values of $t = 0.5$, 0.6, 0.7, and 0.8 were considered, where a higher threshold value indicates less tolerance of dysglycemia.

For each day during the first 14 days of ICU stay, patients were classified by cTIB, threshold, and outcome hospital mortality, yielding a 2×2 contingency matrix for each day [1]. Crucially, this classification was performed independent of the intention-to-treat groups and thus enables the analysis of the association between glycemic level and mortality, regardless of whether the GC was achieved by protocol, natural regulation, or a combination.

$$\begin{array}{c} \\ \text{cTIB} \geq t \\ \text{cTIB} < t \end{array} \begin{array}{c} \begin{array}{cc} L & D \end{array} \\ \begin{bmatrix} N_1 & N_2 \\ N_3 & N_4 \end{bmatrix} \end{array} \tag{1}$$

Table
Patient data shown as median [interquartile range] where appropriate

	SPRINT study	Glucontrol study	All
No. of patients	784	917	1701
Male (%)	61.2	62.9	62.1
Age of patients (y)	65.0 [52.0-74.0]	65.2 [51.5-74.1]	65.0 [51.6-74.0]
APACHE 2 score	18.0 [15.0-24.0]	15.0 [11.0-21.0]	17.0 [13.0-23.0]
Cohort BG (mmol/L)	6.2 [5.3-7.4]	6.9 [5.8-8.4]	6.6 [5.6-8.1]
Per-patient median BG (mmol/l)	6.3 [5.6-7.5]	6.9 [6.1-8.2]	6.6 [5.8-7.9]
% BG in 4.0-7.0 mmol/L	66.8	50.0	56.6
No. of patients with BG < 2.2 mmol/L	36	54	90

The odds of living (OL) given cTIB $\geq t$ are defined as N_1/N_2 and similarly for cTIB $< t$, where N_x represents the number of patients that lived (L) or died (D) for each cTIB state. The OR, defined as the ratio of OL given cTIB $\geq t$ to OL given cTIB $< t$:

$$\text{OR} = \frac{N_1 N_4}{N_2 N_3} \tag{2}$$

Eq. (3) describes the 95% confidence interval (CI) about OR [28]:

$$\left[e^{\ln(\text{OR}) - 1.96 * \sqrt{\frac{1}{N_1}+\frac{1}{N_2}+\frac{1}{N_3}+\frac{1}{N_4}}};\ e^{\ln(\text{OR}) + 1.96 * \sqrt{\frac{1}{N_1}+\frac{1}{N_2}+\frac{1}{N_3}+\frac{1}{N_4}}} \right] \tag{3}$$

For each day of ICU stay, OL and OR, with 95% CI, were calculated for the cohort. The association between glycemic performance (defined by the cTIB metric) and mortality outcome was tested using the χ^2 test with the contingency matrix [1].

3. Results

Fig. 2 shows the OL, by day for the combined cohort for each band and threshold (t). The asterisks indicate a statistically significant ($P < .05$, χ^2 test) association between cTIB $\geq t$ and mortality. Fig. 3 similarly presents the evolution of OR over time with associated CIs.

4. Discussion

Two key factors influence GC in the ICU. First, is the physiological question: Does adequately regulated BG benefit patients? The second, and arguably more difficult, factor is the actual implementation of successful, accurate GC in a busy ICU environment. Van den Berghe et al [7,27] separated these factors by using a specialist nursing team and focused on the physiological question, demonstrating the benefit of GC on patient outcome. A number of studies added weight to this finding by pinning down the pathophysiologic mechanisms and pathways behind glucose toxicity [29–33]. This study is unique in that it analyses the combined results from 2 studies, in normal clinical settings, based on glycemic level, rather than the treatment group. It thus effectively separates physiology from implementation.

It is immediately clear from Fig. 2 that OL given cTIB $\geq t$ is higher than OL given cTIB $< t$ for all values of t, every day, for all 3 glycemic bands studied. Furthermore, Fig. 3 shows that the difference between the odds clearly increased over ICU stay for $t = 0.7$ and 0.8. In each case, the OR tended to increase over ICU stay until day 11. Higher cTIB thresholds resulted in larger increases to OR over time and were particularly significant for the 4.0 to 7.0 mmol/L glycemic band.

This study's results clearly demonstrate a strong association between accurate GC and mortality, regardless of how the glycemic regulation came about. Regulated glycemia was considered equally good whether it was due to a tight GC protocol, endogenous regulation, or a combination. In particular, more time spent within the 4.0 to 7.0 mmol/L glycemic band was associated with higher odds of survival compared with the higher and wider bands.

A possible reason why randomized controlled GC trials yielded conflicting results is that they targeted glycemic level with no means to directly manage variability. These results thus suggest that protocols that directly minimize variability within a specific target band (ie, level and variability) should be prospectively tested to ascertain whether there is a causal relationship with outcome. Hence, this result is not inconsistent with the latest results of the NICE-SUGAR study [10] and other recent reports. Future studies could also examine the ability to achieve given thresholds for specific subcohorts based on diagnosis, organ failure, or other severity score, over time.

An important aspect of this study was the use of the cTIB metric. This metric captures both the level and variability of glycemia, as well as relative exposure to dysglycemia. The cTIB metric was shown to be