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Duration of Time on Intensive Insulin Therapy Predicts Severe Hypoglycemia in the Surgically Critically Ill Population

Nathan T. Mowery · Oliver L. Gunter · Rondi M. Kauffmann · Jose J. Diaz Jr. · Bryan C. Collier · Addison K. May

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Abstract

Background Hypoglycemia has emerged as a barrier to the practice of intensive insulin therapy. Current literature suggests that hypoglycemia occurs at variable rates and has different effects on outcomes in surgical and medical populations. We sought to determine the incidence, independent predictors, and effect on outcome of severe hypoglycemia (≤ 40 mg/dl) in a surgical population.

Methods A retrospective analysis was performed on all critically ill surgical patients treated with IIT from October 2004 to February 2007. Euglycemia (goal 80–110 mg/dl) was maintained using automated computerized titration of an insulin infusion. The primary outcome of interest was any episode of severe hypoglycemia (≤40 mg/dl). Multivariate logistic regression was used to determine the independent predictors of developing severe hypoglycemia.

Results A total of 60,298 data entries (1,118 patients) for glucose were analyzed. There were 64 severe hypoglycemic episodes in 52 patients (4.6% of the patients). There was a significant increase in deaths among patients who experienced at least one episode of hypoglycemia when compared with those who did not (26.9% vs. 15.3%, $P = 0.03$). Logistic regression revealed that the time spent on the protocol was the best predictor of developing a hypoglycemic event when controlling for other known risk factors of hypoglycemia.

Conclusions Intensive insulin therapy can be implemented with a low percentage of patients (4.6%) experiencing severe hypoglycemia. Mortality rate was higher for patients experiencing hypoglycemia. The duration of the time spent on the protocol was the best predictor of hypoglycemia, suggesting that hypoglycemia is a mathematic probability of prolonged illness, not a reflection of illness severity or demographic features.

Introduction

During the last two decades, hyperglycemia increasingly has been recognized as a risk factor for adverse outcomes among patients with acute illness [1]. This association has been shown in a variety of clinical populations including medical and surgical neurologic disease [2–5], acute coronary ischemia and myocardial infarction [6–8], or following cardiovascular surgery [9, 10]. Studies have also identified this same association among heterogeneous populations of patients admitted to adult intensive care units (ICUs) [11, 12]. The American Diabetes Association (ADA) currently recommends that surgical patients be kept at a blood glucose level <110 mg/dl with the nonsurgical population having a goal of <140 mg/dl [13].

The worldwide rapid adoption of tight glucose control in a variety of ICU settings has been brought into question. An increasing number of clinicians have questioned the validity and applicability of tight glucose control to all patients [14, 15]. The NICE-Sugar trial showed harm in attempting tight glucose control [16]. At the center of this

N. T. Mowery (✉)
Department of Surgery, Wake Forest University Medical Center, Medical Center Boulevard, Winston-Salem, NC 27101, USA
e-mail: nmowery@wfubmc.edu

O. L. Gunter · R. M. Kauffmann · J. J. Diaz Jr. · B. C. Collier · A. K. May
Division of Trauma and Surgical Critical Care, Department of Surgery, Vanderbilt University Medical Center, Nashville, TN, USA

controversy is the widespread occurrence of hypoglycemia while attempting to maintain blood glucose levels in the 80–110 mg/dl range. Reports suggest that hypoglycemic events (blood glucose ≤60 mg/dl) may occur in as many as 18.7% of patients managed with intensive insulin therapy (IIT), with the figure being even higher (25.0%) in patients staying in the ICU longer than 5 days [17]. There appears to be an unavoidable increase in the rate of severe hypoglycemia (SH), defined as a glucose level ≤40 mg/dl, among patients treated with IIT [18, 19]. The termination of two large prospective randomized trials in Europe due to the incidence of hypoglycemia has fueled the debate about the safety in tight glucose control [20, 21].

The effect that these hypoglycemic episodes have on outcome and their predictive factors is still being determined. Krinsley and Grover found that a single episode of severe hypoglycemia conferred an increased risk of mortality in a mixed medical and surgical ICU [22]. Other authors have found that hypoglycemia did not independently increase the risk of mortality [23]. In other cases, the same authors found opposing effects on outcomes in different populations. Van den Berghe et al. found that in a predominantly surgical population [24] hypoglycemia was not associated with adverse outcomes but in a medical population [17] hypoglycemia was independently associated with an increased risk of mortality. What is unknown is whether SH plays a causal role in mortality or other adverse outcomes or is merely a marker for overall illness severity. Also, it is uncertain whether a low rate of adverse events related to SH may be outweighed by improvements in the rates of mortality and secondary complications previously associated with IIT.

Studies to date have looked at hypoglycemia in mixed medical/surgical ICUs. The net effect of tight glucose control has not been reproducible from surgical to medical ICUs. The goal of this study was to determine factors predicting severe hypoglycemic events (≤40 mg/dl) and to evaluate the effect of hypoglycemia on outcome in surgically critically ill patients.

Materials and methods

All critically ill, mechanically ventilated patients admitted to the Surgical Intensive Care Unit (SICU) of Vanderbilt University Medical Center are managed with a tight glycemic control strategy that employs intravenous insulin administration for patients with glucose levels >110 mg/dl and repeated glucose sampling every 2 h, with insulin adjustments. All values for glucose, insulin, and an adapting multiplier are prospectively captured into a computerized order entry system as described below.

Study population

Inclusion criteria for IIT were (1) admission to the SICU, (2) mechanical ventilation, and (3) a serum blood glucose value >110 mg/dl. There were 2,578 patients admitted to the SICU over the study period, which ran from October 2004 through February 2007. A total of 1,118 patients were treated with the IIT protocol during the study period.

The study ICU is a 21-bed "semiclosed" unit at a university teaching hospital. The population is composed exclusively of surgical patients (excluding cardiac bypass and neurosurgical patients) and is under the direct care of the ICU team. Trauma patients were not included in this data set as they are cared for in a separate location at our institution. The ICU team comprises seven full-time intensivists, three subspecialty fellows, and a rotating team of two residents.

In all, 73 of the 1,118 patients stayed in the SICU for less than 1 day. Those "short stay" patients were from a variety of services. A total of 817 of the 1,118 patients were placed on the protocol on the 1st day of their hospital admission. The mean time to initiation of the protocol for the entire group was 2.2 days.

Insulin protocol

Vanderbilt University developed a computerized care provider order entry (CPOE) system that facilitates the maintenance of euglycemia (blood glucose 80–110 mg/dl) using an intravenous insulin infusion. The adjusted insulin dose is determined by a linear equation that utilizes an adaptable multiplier (M) based on the glucose response from the previous dosing period. The adaptability of M to varying physiologic demands throughout a patient's hospitalization is a key characteristic of the protocol. The insulin dose is calculated using the formula:

$$\text{Insulin dose (units/hr)} = (\text{multiplier}) * [\text{blood glucose (mg/dl)} - 60]$$

M is initially set at 0.03 and can never fall below zero. The insulin dose is altered by the use of an adapting multiplier that is controlled by a set of rules [25]. The protocol's titration description has been shown to be an effective means of maintaining euglycemia with a low rate of hypoglycemic events [25, 26]. The data collection for this data set ended when the patient was transitioned to sliding scale insulin. This occurred when a stable dose of insulin had been reached and the patient's clinical picture stabilized or when the patient was transferred from the SICU.

On admission, all patients are started on a glucose source consisting of intravenous dextrose (D5 or D10) to

deliver partial nutritional support (5–10 g/h) unless enteral or parenteral feeding is being delivered. Enteral nutritional support is initiated as soon as the attending physician believes it to be safe. Parenteral support is initiated on day 5 of the patients' ICU stay if 70% of the goal nutrition cannot be attained enterally and continued until enteral support is adequate. Nutrition goals have been established according to published standards with 20–24 nonprotein kilocalories per kilogram of body weight per 24 h [27]. The glucose or nutritional source is prospectively captured in the CPOE.

Data collection

The patient's sex, age, body mass index (BMI), dates of hospital and ICU admissions, hospital mortality, requirement for vasopressor therapy, history of diabetes, and pharmacy data were obtained from electronic hospital records and databases. Information necessary to determine the severity of illness, including the Acute Physiology, Age, and Chronic Health Evaluation (APACHE) II score [28] was obtained at admission and recorded in an institutional database. The APACHE II score was used as a measure of severity of illness.

Blood glucose measurements are performed according to a protocol by a member of the nursing staff using the SureStep Pro (One-Touch) Professional Blood Glucose Monitoring System (http://www.lifescan.com/professionals/products/sspro/). Arterial samples were used when an arterial line was available, which was 99.7% of the time; otherwise a fingerstick sample was taken. Measurements were taken at 2-h intervals with the exception of following hypoglycemic events (blood glucose <60 mg/dl), which trigger a repeat measurement within 1 h. The IIT CPOE produced entries that consist of a blood glucose value, multiplier value, insulin dose, glucose source, and the time, date, and treatment of hypoglycemia.

Outcome measures

The primary outcomes of interest were any episode of severe hypoglycemia (<40 mg/dl) and all-cause in-hospital mortality. Secondary outcome measures were hospital length of stay, ICU length of stay, and ventilator days.

Statistical analysis

Normally distributed continuous variables were summarized by reporting the mean and standard deviation and compared using two sample t tests for independent samples. Continuous variables that were not normally distributed were presented by reporting the median and interquartile ranges (IQRs) and compared using the Mann–Whitney U test. Differences in proportions were compared using a χ^2 test or Fisher's exact test. Multivariate logistic regression was used to estimate the independent relation between risk factors and episodes of severe hypoglycemia. A two-sided $P < 0.05$ was considered to indicate statistical significance. SPSS version 15.0 (SPSS, Chicago, IL, USA) was used for analysis.

The institutional review board of Vanderbilt University Medical Center approved the study. All data were maintained in a secure, password-protected database that is HIPAA-compliant. All patient information was de-identified prior to analysis and reporting.

Results

On admission, 123 of 1,118 (11.0%) of the patients had a past medical history of diabetes, with 108 of the 123 (87.8%) of the diabetics having non-insulin-dependent diabetes (NIDDM) and 15 (12.2%) having insulin-dependent diabetes (IDDM). As a group, the mean age was 58 ± 15 years, and the mean APACHE II score was 18 ± 6. The mortality rate for the group was 15.8% (177/1,118). The median glucose for the entire group was 121 mg/dl (IQR 111–142). There were 64 episodes of severe hypoglycemia (≤40 mg/dl) documented for 18,890 patient-days and 60,298 glucose values (Table 1). Patients were next grouped into those experiencing severe hypoglycemia and those who did not have a severe hypoglycemic event during their admission. Demographic features (age, history of diabetes, BMI) did not differ between patients experiencing hypoglycemic events and those who did not (Table 2).

Blood glucose control

There were 60,298 blood glucose values with corresponding insulin indices available for analysis (Table 3). The admission blood glucose was not significantly different between those who experienced SH and those who did not (155 vs. 158 mg/dl, $P = 0.99$). The median value for each of the groups was calculated by taking the median of the individual patient's blood glucose values. The median blood glucose was not statistically different between groups (119 mg/dl for no SH and 118 mg/dl for SH, $P = 0.45$). The median insulin dose was lower in the hypoglycemic group but not by a significant amount (3.2 vs. 3.7 U/h, $P = 0.21$). The mean multiplier was higher in nonhypoglycemic patients than in those who were hypoglycemic (0.047 vs. 0.042; $P = 0.03$). The patient who had SH spent significantly more time on the IIT protocol and in the hospital, evidenced by their longer ventilator days, ICU stay, hospital stay, and more data points on the protocol.

Table 1 Demographic data of study population

Parameter	Data
Age (years), median	58.1 (IQR 49–67.6)
Sex	
Male	631 (57%)
Female	487 (43%)
APACHE II	18.2 ± 6.0
Blood glucose (mg/dl), mean ± SD	131 ± 33
Insulin dose (units/hr), mean ± SD	4.3 ± 2.4
Type of surgery	
General	533 (47.7%)
Liver transplant	191 (17.1%)
Thoracic	121 (10.8%)
Vascular	108 (9.6%)
Orthopedic	50
Urologic	42
ENT	31
Gynecologic	29
Plastic	13
Hospital LOS (days), median	11.3 (IQR 7–21)
ICU LOS, median	4.4 (IQR 2–10.4)
Hospital mortality	177 (16%)

IQR interquartile range, *APACHE* acute physiology, age, and chronic health evaluation, *ENT* ear/nose/throat, *LOS* length of stay in hospital, *ICU* intensive care unit

Table 2 Demographic features of study groups

Parameter	Hypoglycemia ($n = 52$)	No hypoglycemia ($n = 1066$)	P
Age (years)	53 (34–67)	56 (43–66)	0.37
Sex (female)	22 (42%)	435 (41%)	0.94
APACHE II	18 (14–22)	18 (13–22)	0.88
History of diabetes	9 (9.7%)	142 (10.2%)	0.87
BMI	24.1 (21.4–29.1)	25.7 (21.2–30.8)	0.06

Data are represented as median (IQR) unless otherwise noted

BMI body mass index

Hypoglycemia rate

The median time to the first SH event was 87 h (IQR 19–173). Hospital mortality was higher among patients with SH than among those without: 26.9% vs. 15.3%, $P = 0.03$.

Relation of infections to hypoglycemia

In all, 33 of the 52 patients who experienced severe hypoglycemia had a positive culture. A blood sample was obtained for culture in 8 of these 33 patients that was positive in the 48 h before or after their episode of severe hypoglycemia. One patient had two hypoglycemic episodes during the 48 h before her *Acinetobacter* pneumonia was identified.

Table 3 Hospital features of study groups

Parameter	Hypoglycemia ($n = 52$)	No hypoglycemia ($n = 1066$)	P
Insulin dose (units/h)	3.2 (2.5–4.9)	3.7 (2.5–5.3)	0.21
Vasopressor use	41 (78.8%)	733 (68.8%)	0.15
Maximum creatinine (mg/dl)	1.7 (1.0–3.0)	1.5 (1.0–2.5)	0.22
Ventilator days	14 (7–29)	3.0 (1–9)	<0.001
ICU days	13 (6–26)	4 (2–10)	<0.001
Hospital days	23 (11–43)	11 (7–20)	<0.001
Hospital mortality	14 (26.9%)	163 (15.3%)	0.03

Data are represented as the median (IQR) unless otherwise noted

Multivariate regression for hypoglycemia

A regression model was built with known risk factors for hypoglycemia (Table 4). We included the number of data points on the protocol to control for the duration on the protocol. Logistic regression revealed that the time spent on the protocol was the best predictor of developing an SH event when controlling for other risk factors of hypoglycemia [odds ratio (OR) 1.02, 95% CI 1.07–1.15, $P < 0.001$]. Furthermore, when controlling for the time spent on the protocol, risk factors that have previously been shown to correlate with SH were no longer significant.

Discussion

The current study shows that SH is not associated with specific demographic factors in surgical patients but is, rather, a statistical by-product of the time spent on the protocol. This differs from other studies predicting determinates of hypoglycemia that have been done on mixed medical/surgical patients. Other studies have referenced the duration of the glucose control protocol and various demographic factors associated with an increased incidence of hypoglycemic events [22, 29]. The current work is the largest study examining hypoglycemia in an exclusively surgical population, which highlights the importance, as previous studies have alluded to, that the incidence of hypoglycemia differs between surgical [24] and medical [17] populations.

Studies continue to report a higher incidence of hypoglycemia when a goal range of 80–110 mg/dl is targeted;

Table 4 Multivariate regression of predictors of hypoglycemia

Predictor	Odds ratio	95% CI	*P*
Data points	1.007	1.002–1.007	0.006
APACHE II	1.016	0.897–1.151	0.799
Age (years)	1.039	0.983–1.097	0.177
BMI	0.922	0.809–1.050	0.221
History of diabetes	0.379	0.09–1.64	0.20
On a vasopressor	0.671	0.076–5.912	0.720

CI confidence interval

however, there is a great amount of variability in the incidence of hypoglycemia being reported. Virtually all large studies comparing a tight versus a liberal glucose control range have shown that the incidence of hypoglycemia is higher when targeting a lower goal range of 80–110 mg/dl [17, 20, 21, 24]. This incidence can be as high as 18.7%, as was found in the second Leuven study, which was conducted among medical ICU patients [17]. Both the VISEP study ($n = 488$), carried out on septic medical patients, and the GLUControl study ($n = 1{,}108$), which were designed to validate the first two Leuven studies, were prematurely stopped owing to concerns about hypoglycemia. There have been other studies showing that instituting tight glucose control does not increase hypoglycemia, but this is only when compared to historical controls [30]. Although the current round of studies examining glucose control have brought the range for which we should be aiming in question, none has advocated abandoning glucose control entirely. All have reported episodes of hypoglycemia even with more modest goals of 150 or 180 mg/dl. The current protocol showed only a 4.6% rate of hypoglycemia with similar mean glucose values between patients who experienced SH and those who did not. Interestingly, it is more in accordance with the first Leuven [24] study's rate of 5.1%, which was also conducted on a surgical population and was lower than in the intensive arms of the other studies that included predominantly medical patients (Table 5).

A variety of risk factors have been identified predisposing patients to the development of hypoglycemia in a mixed medical and surgical ICU. Vriesendorp et al. [29] identified female sex, the presence of preexisting diabetes, sepsis, the use of continuous venovenous hemofiltration (especially with bicarbonate-based substitution fluid), lowering of the infusion rate of nutrition without adjusting the insulin infusion rate, and the administration of insulin by itself as independent risk factors for hypoglycemia. The glycemic target for this group was 81–144 mg/dl; 6.9% sustained at least one episode of SH. Krinsley identified essentially the same risk factors with the addition of the severity of the illness (represented by a modified APACHE II score: the age component was deleted) as risk factors for the development of severe hypoglycemia [22]. Interestingly, 27.5% of the patients in that study were not on insulin before developing hypoglycemia. Most of the patients in the Krinsley study were being controlled without an insulin drip and, instead, using subcutaneous insulin, which has been shown to have variable absorption in the critical care setting [31]. Arabi et al. confirmed these risk factors in a mixed population documenting the same risk factors for hypoglycemia [19]. Our study did not show sex, age, preexisting diabetes, APACHE II score, or renal failure as predictors of hypoglycemia in our surgical population in the univariate or multivariate analyses. These differences may be due to variation in the patient population. In general, this study group was younger, had a lower APACHE II score, and had more male participants than other studies examining hypoglycemia. This purely surgical population had a much lower incidence of diabetes than the other mixed medical/surgical cohorts. For example 9.7% of the patients experiencing SH in our cohort were diabetic, compared to 47.1% of the patients in Krinsley's SH cohort [22]. These differences highlight the unique demographic features typical of a surgical subset. The differences in outcomes found in this study may caution the applicability of research done in nonsurgical patients to surgical patients.

Table 5 Incidence of hypoglycemia in various studies

Study	Population	Hypoglycemia in 80–110 mg/dl arm (%)
Current study	Surgical	4.6
Van den Bergh 2001	Surgical, cardiac	5.1
Van den Bergh 2006	Medical	18.7
VISEP	Medical	17
NICE-SUGAR	Mixed	6.8
GLUControl	Mixed	12.1
Krinsley 2007	Mixed	1.9 (goal 80–125/<140 mg/dl)
Vriesendorp 2006	Mixed	6.9

Few studies have accounted for the length of stay as a factor in hypoglycemia rate. Vriesendorp et al. made an attempt to control for length of stay in hospital (LOS) by matching index cases to patients selected from a control group based on length of stay before the development of hypoglycemia. These investigators examined only the first episode of hypoglycemia and did not examine the risk of developing multiple episodes of hypoglycemia [29]. The VISEP trial documented a trend toward a longer stay for patients in the intensive glucose control arm of the study. They were unable to determine if the longer stay was a

direct effect of the hypoglycemic episodes but inferred it in their study [20]. Arabi and colleagues also reported that ICU LOS (measured in days) was an independent predictor of the incidence of hypoglycemia [19]. In the current study, we also found the time on the protocol to be an independent predictor of hypoglycemia. Given the retrospective nature of these data and the ethical dilemma with randomizing patients to hypoglycemia, it remains difficult to resolve whether hypoglycemia causes a longer LOS or if patients with a longer LOS have an increased probability of becoming hypoglycemic.

Hypoglycemia is not benign in critically ill patients; it has been linked to serious neurologic events ranging from seizures to coma [23, 32]. The current study did identify a significant difference in mortality in a univariate analysis. Multiple large series have been split on their ability to document an effect on mortality when attempting tight glucose control, with some showing no effect [19, 23, 24] and others documenting hypoglycemia as an independent predictor of mortality [17, 20–22, 33, 34]. The NICE-SUGAR study certainly supports the notion of increased hypoglycemia with IIT. This relation was seen in both the medical and surgical subsets of the larger study group. The authors pointed out that there were no sequelae that were attributed to these episodes of hypoglycemia [16]. Our group has examined the incidence and effect of hypoglycemia in the trauma population and did not find it to be an independent predictor of mortality [35]. The reasons for the discrepancies between these studies are unknown, although the study design may be a significant factor [36–38]. In the studies documenting no effect of hypoglycemia, the intervals for monitoring the blood glucose were short, implying that the duration of the hypoglycemic episodes were not prolonged. Therefore, the possibility that a longer duration of hypoglycemia may be deleterious or even life-threatening cannot be ruled out. Regarding the consequences of non-life-threatening hypoglycemia, long-term cognitive and other neurologic impairments have been reported, although this has yet to be described in critically ill patients experiencing short-term episodes of hypoglycemia [23]. The 52 patients in this study who experienced SH were reviewed as part of our ICU morbidity and mortality conference. In no case of SH while on the protocol in the SICU has any patient had a documented change in neurologic examination or change in clinical condition directly associated with the hypoglycemia.

We also attempted to examine the 64 hypoglycemic episodes individually to determine if a direct etiology could be identified. We examined the time period surrounding the episodes to see if the glucose source was altered or there were insulin protocol violations. None was identified in this data set. Determining these items retrospectively with any reliability using the electronic medical record was questionable. Pauses to change maintenance intravenous fluids or swap empty enteral feeds were not recorded in the electronic medical record. It is not the unit's policy to pause the glucose source when traveling to the operating room or radiology, but it could have happened. We attempted to correlate trips to the operating room and the time stamp on radiologic tests with hypoglycemic episodes and could not find a temporal correlation. The fact that the mean glucose level preceding a hypoglycemic episodes was 118 $\pm$ 40 mg/dl and the low incidence overall suggest that the insulin protocol was not the cause of severe hypoglycemia. These data were unable to identify the exact cause of individual episodes of severe hypoglycemia.

Others have used this fear of hypoglycemia to advocate for a more liberal range (80–150 mg/dl). Earlier work examining glucose control clearly showed that the mortality rate was lower as the mean glucose level decreased [39, 40]. Based on the data of the two Leuven studies [17, 24] that reported an improved outcome when insulin therapy was titrated to achieve a range of 80–110 mg/dl, rather than 180–200 mg/dl, a blood glucose of >180 mg/dl can probably no longer be considered an acceptable target for insulin therapy in critically ill patients. The fact that the NICE-Sugar investigators chose a goal of <180 mg/dl for the liberal arm suggests that these authors thought the blood glucose should not be allowed to remain above this level in the critically ill. Three large retrospective trials [30, 39, 41] found that blood glucose levels of <140 mg/dl (7.78 mmol/l) were associated with improved outcome as compared to higher levels. It appears that the current literature supports the ADA recommendations that surgical and medical patients have different goals [13]. The ADA recommendations to target a blood glucose level as close to 110 mg/dl as possible, and generally <140 mg/dl, appear to be largely based on the first Leuven [24] study, which remains the most appropriate reference for glucose control in a surgical population. Targeting these lower ranges, however, would continue to put surgical patients at risk for hypoglycemia.

One potential explanation in the difference between the current work and other large series was the inclusion of medical ICU patients. This study consisted mostly of nondiabetic patients undergoing surgical procedures. The exact physiologic differences between surgical and non-surgical patients remain difficult to quantify. Perhaps the inflammatory response seen after surgery or injury exacerbates the detrimental effects of hyperglycemia or is in some way protective during episodes of hypoglycemia. There continues to be emerging belief that the benefits of intensive glucose control are not universal but specific to certain patient populations. The original Leuven study and new meta-analysis suggest that surgical patients are most likely to benefit from tight glucose control [42, 43].

The future of intensive glucose control may well be a more tailored approach to different patient populations, with different groups having different ranges.

Conclusions

Intensive insulin therapy can be implemented in surgical patients, with a low percentage of patients (4.6%) experiencing severe hypoglycemia. Although the incidence may be low, there appears to be an association with an increased mortality rate among patients experiencing hypoglycemia, suggesting that strict monitoring and correction is essential when adhering to tight glucose protocols. The duration of the time spent on the protocol was the best predictor of hypoglycemia, suggesting that hypoglycemia is a mathematic probability of prolonged illness, not a reflection of illness severity or demographic features in the surgical population.

Conflicts of interest The authors declare that there are no conflicts of interest.

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