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Time and degree of glycemic derangement are associated with increased mortality in trauma patients in the setting of tight glycemic control

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Time and degree of glycemic derangement are associated with increased mortality in trauma patients in the setting of tight glycemic control

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Abstract

BACKGROUND: Tight glucose control (TGC) may reduce mortality in critically ill trauma patients. We hypothesize that euglycemia is beneficial, and a measure considering time and degree of hyperglycemia is most associated with mortality.

METHODS: We performed a review of intensive care unit trauma patients admitted for more than 3 days between January 2005 and December 2007 on a TGC protocol with a goal of 80 to 110 mg/dL. Hyperglycemic, hypoglycemic, and euglycemic time ranges, and area of interpolated curves above and below 80 to 110 mg/dL were assessed. Associations with mortality were based on logistic regression models adjusted for age, injury severity score, and admission Glasgow Coma Scale score.

RESULTS: A total of 546 patients were identified, and 68 (13%) died. Time spent as hyperglycemic ($P = .29$) and hyperglycemic area under the curve ($P = .58$) were not associated with mortality; hyperglycemic area/time ($P = .01$) was associated with mortality. Regarding hypoglycemia, area over the curve ($P = .009$) and time spent as hypoglycemic ($P = .002$) were associated with mortality.

CONCLUSIONS: TGC prevents prolonged, high degrees of hyperglycemia; avoiding hypoglycemia likely provides mortality benefit for trauma patients.

Stress hyperglycemia occurring in critically ill intensive care unit (ICU) patients has a well-documented association with morbidity and mortality.[1,2] The association between high blood glucose and increased mortality has been shown in patients after trauma,[3–9] burn,[10] cardiac surgery,[11,12] myocardial infarction,[13–16] and stroke,[17,18] as well as for general ICU patients.[19–21] Increased blood glucose levels above the normal range of 80 to 110 mg/dL are common in a wide variety of acute illnesses, irrespective of previously

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diagnosed diabetes.[13,17,20,22] In an effort to mitigate the effects of hyperglycemia, tight glucose control protocols have been implemented in ICUs worldwide.[23–29] Common to these protocols is use of insulin to try to convert a hyperglycemic patient to a normoglycemic patient. There is wide inconsistency, however, in the methods used to describe glucose control and in the glucose end point, which showed a mortality or morbidity improvement. In her landmark study, Van den Berghe et al[30] measured 6 AM glucose level to assess glycemic control. Since then, admission ICU glucose level,[4,7,31] average daily glucose level,[9] maximum glucose level,[4] average overall glucose level,[4,20] and time in range[29,32] also have been used to assess glycemic control. However, other investigators have found that these results have not been consistent.[33,34] Volgelzang et al[35] support the idea that there are potentially inherent deficiencies in these methodologies, for instance, the use of mean glucose concentration as a predictor of morbidity and mortality likely incurs bias because of unequal time distribution between measurements. They described use of the "hyperglycemic index,"[35] which measures the area between the upper limit of normal and the curve of interpolated glucose values above the normal range, to show that area under the curve has a superior relation with mortality compared with other glucose indexes. However, this methodology does not incorporate hypoglycemia and has not been applied to critically ill patients routinely placed on a tight glucose control (TGC) protocol. Thus, we hypothesize that a measure that includes both time and degree of glycemic derangement eliminates the bias of using each independently and would better predict mortality than either would alone in a setting of routine TGC.

Methods

This was a single-center, retrospective review of patients age 18 years and older admitted after a trauma to University Hospital (San Antonio, TX), a Level I Trauma Center, between January 2005 and December 2007. The surgical trauma ICU has had a TGC protocol in place since 2005. Subjects were identified by trauma registry query and blood glucose values were obtained by query of the hospital electronic medical record. Patients with an injury severity score (ISS) of less than 9 and an ICU length of stay of less than 3 days were excluded. The study protocol was approved by the UTHSCSA Institutional Review Board. We collected all glucose values, demographics, diagnoses, mechanism of injury, medical history including diabetes, length of ICU stay, clinical course, and disposition. Hyperglycemia was defined as any value greater than 110 mg/dL; hypoglycemia was defined as less than 80 mg/dL. Severe hypoglycemia was defined as 40 mg/dL or less regardless of symptoms or lack thereof. Glucose parameters assessed were ICU admission values; average morning glucose level (6:00 AM reading); average daily glucose level; amount of time in the hyperglycemic, hypoglycemic, and euglycemic ranges; and area hyperglycemic (area under interpolated curves above 110 mg/dL) and area hypoglycemic (area over interpolated curves below 80 mg/dL). A representative curve is shown in Fig. 1.

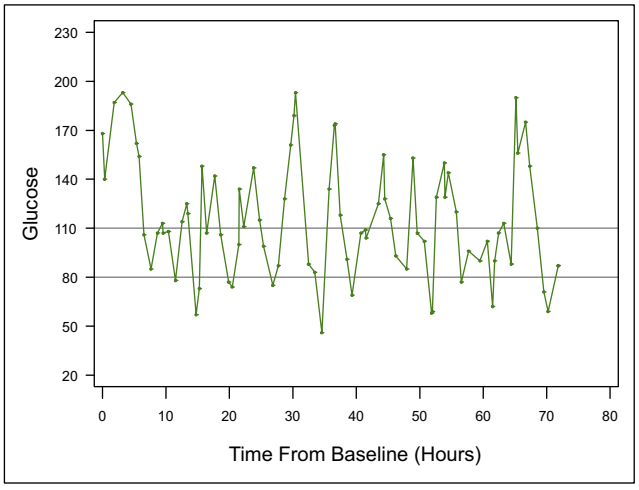

Figure 1 A typical interpolated curve from which areas and times were calculated.

We used logistic regression models to assess associations between glucose measures and mortality with and without adjustment for age, ISS, and admission Glasgow Coma Scale (GCS) score. Associations were made based on the first 72 hours of ICU stay so that all patients contributed to the logistic regression model and to avoid survivor bias. We summarized continuously distributed outcomes by the mean ± 1 standard deviation or the median and the first and third quartiles and contrasted survivors with nonsurvivors using Wilcoxon tests. We contrasted survivors with nonsurvivors on binary outcomes with the Fisher exact test. All statistical testing was 2-sided with a significance level of 5% and SAS version 9.2 for Windows (SAS Institute, Cary, NC) was used throughout.

TGC protocol

At admission to the surgical ICU, all patients received 3 point-of-care capillary fingerstick glucose tests 4 hours apart. If 1 value was greater than 150 mg/dL or 2 values were greater than 120 mg/dL, the patient was started on a continuous intravenous insulin infusion to keep blood glucose values between 80 and 110 mg/dL. Blood glucose level was checked hourly on the insulin drip and adjusted until it remained stable for 4 hours. Once stable, the blood glucose level then was checked every 2 hours. Point-of-care glucose testing was performed by medical technicians using the Accu-Chek Inform System (F. Hoffmann-La Roche, Ltd, Basel, Switzerland). Insulin therapy was held for glucose values less than 70 mg/dL, and dextrose was administered for values less than 50 mg/dL. Regarding nutritional ther-

apy, the standard of care in the ICU was to institute enteral feeding as soon as possible.

Results

Demographics

A total of 546 subjects were identified. Most patients were male (69%; 378 of 546), with a mean age of 50 years (standard deviation, 20.2 y). The proportion of patients with a history of diabetes (Table 1) was similar between survivors and nonsurvivors (24% survivors and 27% nonsurvivors; $P = .65$). Presence of head injury was significantly higher in nonsurvivors (62%) compared with survivors (48%; $P = .04$). Average admission GCS was significantly lower in the nonsurvivors (7.7 ± 5.5) when compared with survivors (10.3 ± 5.3; $P < .001$). ISS scores were significantly higher in the nonsurvivors (31.7 ± 12.7) compared with the survivors (24.4 ± 10.2; $P < .001$), as well as Trauma Injury Severity Score (TRISS) (.5 ± .4 and .7 ± .3, respectively; $P < .001$). There were 68 deaths for an overall mortality rate of 13% (68 of 546). Of these, 21 of 68 were declared dead according to neurologic criteria.

Glucose measurements

A total of 97,846 glucose measurements were analyzed with a median of 102 (range, 45–241) measurements per subject. The median number of daily glucose measurements per subject was 6.5 (range, 3.9–11.3). ICU admission glucose level was similar between survivors and nonsurvivors.

Table 1 Demographics by outcome

	Survivors n = 478	Nonsurvivors n = 68	*P* value
Age, y*	49.2 ± 19.6	55.5 ± 23.3	.03
Male, n (%)†	328 (68.6)	50 (73.5)	.48
History of diabetes, n (%)†	112 (23.5)	18 (26.5)	.65
Traumatic brain injury, n (%)†	229 (47.9)	42 (61.8)	.04
Admit GCS*	10.3 ± 5.3	7.7 ± 5.5	<.001
ISS*	24.4 ± 10.2	31.7 ± 12.7	<.001
TRISS*	.7 ± .3	.5 ± .4	<.001
Injury type†			
Blunt, n (%)	449 (94.1)	63 (92.6)	.59
Penetrating, n (%)	28 (5.9)	5 (7.4)	
Hospital length of stay, d*	17 (10–27)	8 (5.5–17.5)	<.001
ICU length of stay, d*	8 (4–16)	8 (5.5–17)	.39
Days on ventilator*	3(0–11)	7.5 (4–12)	<.001

Values in ( ) are ranges unless otherwise noted.
*Wilcoxon test.
†Proportion; compared using the Fisher exact test.

Table 2 Glucose value characteristics by outcome

	Survivors n = 478	Nonsurvivors n = 68	*P* value*
Admission glucose level	176 (83.4)	186.9 (84.3)	.12
Average daily glucose level†	118.4 (31.7)	122.1 (53.5)	.95
ICU average length of stay glucose level†	116 (98–146)	108 (94–139.5)	.35
Maximum glucose level†	215.2 (80.1)	239.6 (101)	.01
Minimum glucose level†	71.7 (19.4)	66.9 (23)	.04

Survivor and nonsurvivor values are expressed as mean (SD or range).
*Wilcoxon test.
†First 3 days.

In the first 3 days, morning glucose level and average daily glucose level did not vary significantly between survivors and nonsurvivors (Table 2); the maximum glucose level was increased significantly ($P = .01$) and the minimum glucose level was decreased significantly in nonsurvivors ($P = .04$).

Logistic regression model

Regarding hyperglycemia, neither area under the curve (AUC) as hyperglycemic (AUC, .739; $P = .58$) nor total time spent as hyperglycemic (AUC, .739; $P = .29$) were associated with mortality. However, the ratio of area/time spent hyperglycemic was associated significantly with mortality (AUC, .745; $P = .01$).

Regarding hypoglycemia, both AUC as hypoglycemic (AUC, .752; $P = .009$) and time spent as hypoglycemic (AUC, .758; $P = .002$) were associated significantly with death, but the ratio of area over time spent as hypoglycemic was not (AUC, .717; $P = .26$) (Table 3).

Table 3 Associations between mortality and glucose time and area summary measures

Measure	Odds ratio (95% CI)	AUC*	*P* value
Area hyperglycemia	1.00 (1.00–1.00)	.739	.58
Time hyperglycemia	.991 (.975–1.008)	.739	.29
Area hyperglycemia/time	1.016 (1.004–1.029)	.745	.01
Area hypoglycemia	1.004 (1.001–1.007)	.752	.009
Time hypoglycemia	1.063 (1.023–1.104)	.758	.002
Area hypoglycemia/time	1.039 (.971–1.112)	.717	.26

Associations for the first 3 days adjusted for age, ISS, and admission GCS score.
*AUC; area under the receiver operator characteristic curve.

Hypoglycemia

There were 1,139 hypoglycemic (<80 mg/dL) values in 373 of 546 (68%) patients in the first 3 days. Over the entire hospital stay, 4.8% (4,692 of 97,846) of glucose values were less than 80 and 458 of 546 (84%) individual patients had at least 1 value less than 80. Severe hypoglycemic (≤40 mg/dL) values were fewer: 42 glucose values in 32/546 individual patients, a rate of 5.9% in the first 3 days. Over the entire hospital stay, .14% (140 of 97,846) of glucose values were 40 mg/dL or less and 89 of 546 (16%) individual patients had at least one value of 40 or less.

Conclusions

The use of TGC protocols in the care of critically ill patients has resulted in much effort, research, and expense since it was first identified that TGC may contribute to an improvement in mortality rate in critically ill patients. In this study, we hypothesized that both the overall degree of hyperglycemia and the time spent as hyperglycemic combined were associated with mortality and that independently these measures were not. The use of AUC calculations in a critically ill population was first introduced by Volgelzang et al[35] as the hyperglycemic index. However, the subjects in their study were not routinely placed on a strict glucose control protocol. In addition, the hyperglycemic index did not apply to or quantify hypoglycemia, which is represented in our calculations as AUC. Thus, our results reflect a contemporary population of critically ill trauma patients who had been routinely placed on a TGC protocol.

Although other investigators have shown that time spent as hyperglycemic is associated with mortality, our data did not show this association.[29,32] We explain this by considering that time spent as hyperglycemic taken by itself does not give the full picture of a patient's physiology because equally timed excursions out of range are not quantified as large or small. Similarly, if comparing 2 patients with equal hyperglycemic AUCs, small derangements over a long time would be the same as large derangements over a short time. These patients likely would have very different physiologies and different mortality expectations. By indexing area/time spent as hyperglycemic, the degree of derangement per unit of time can be quantified, hence the finding that a high degree of hyperglycemic derangement/time is associated with mortality.

Regarding hypoglycemia, time spent as hypoglycemic was associated with mortality, suggesting that any amount of time spent hypoglycemic was detrimental. Area hypoglycemic also was predictive of mortality, suggesting that any hypoglycemia that a patient incurred was detrimental. That area/time was not predictive of mortality suggests that it is not the degree per unit of time that impacts mortality, but any hypoglycemia at all. The finding that any hypoglycemia (<80 mg/dL) is associated with mortality is noteworthy because hypoglycemia usually is considered clinically significant at less than 40 mg/dL or with significant sequelae such as seizures, cardiac dysrhythmia, or coma. That 3 recent large studies ceased enrolling patients before completing enrollment goals owing at least in part to high rates of hypoglycemia illustrates the concern that all hypoglycemia may be detrimental in critically ill patients.[36] The rates of severe hypoglycemia (≤40 mg/dL) encountered overall in our study (16%) were much higher than the 8.7% rate reported in the GluControl trial or the 6.8% reported in the Normoglycemia in Intensive Care Evaluation–Survival Using Glucose Algorithm Regulation (NICE-SUGAR) trial; although the rate during the first 3 days, 4.8%, is consistent with these other studies.[37,38] Although 16% may seem comparatively high at first glance, these values are not indexed by number of patient days or presented as a proportion of total glucose values obtained. When considered as a proportion of total glucose values, our rate of hypoglycemia (≤40 mg/dL), .14% (140 of 97,846), is quite low.

Based on our data, we propose that an ideal TGC protocol for critically ill trauma patients admitted to the ICU for longer than 3 days would avoid large hyperglycemic excursions, but allow for much smaller excursions throughout the ICU stay and avoid any hypoglycemia. To achieve this, we suggest that the ideal TGC protocol must control increased glucose values aggressively and early with screening and liberal use of intravenous insulin drips and then address increased glucose levels throughout the hospital stay before they become large excursions. Furthermore, to reduce the amount of hypoglycemia, the goal range must have a greater lower control limit. The resulting protocol would aim for a higher lower limit such as 100 mg/dL and increase the difference between the upper and lower limits of normal from 30 mg/dL to perhaps 50 mg/dL such that rather than 80 to 110 mg/dL, the range would become 100 to 150 mg/dL. The resulting glucose curve would have fewer significant excursions from control.

These recommendations are speculations based on our data and would need to be tested in a similar population to ours. It must be kept in mind that our TGC protocol is designed with the intention of maintaining glucose levels between 80 and 110 mg/dL, and our subject's glucose values were influenced by patient physiology, critical illness, and insulin dosing behavior to keep glucose values in the 80 to 110 mg/dL range.

Although the range of 80 to 110 mg/dL has largely become the standard, increased incidences of hypoglycemia have caused investigators to challenge this glycemic goal.[36–38]

Recognizing that the prospective randomized trials after Van den Berghe et al[30] trial have failed to produce the same mortality reduction and that the ideal range for blood glucose level in critically ill patients is unclear, the NICE-SUGAR study investigators compared mortality in patients on a TGC regimen with a range of 81 to 108 mg/dL with a conventional glucose control range of less than 180 mg/dL. Based on a primary end point of 90-day mortality, they showed that there was a statistically significant increase in

mortality associated with their TGC protocol and glucose range. They also reported a significantly higher rate of severe hypoglycemia (≤40 mg/dL) in the TGC group (6.8% vs .5%). The investigators concluded that "intensive glucose control increased mortality among adults in the ICU."[38] Although the data in the NICE-SUGAR study well showed that the protocol used to achieve conventional glucose control was superior to the one used to achieve TGC, this study compared only 2 protocols and glucose ranges. Certainly, both achieved better control than would have been achieved without a protocol, but the rate of hypoglycemia in the tight control group was an order of magnitude higher than in the conventional group. It could be that any benefit that was achieved by TGC was mitigated by the impact of hypoglycemia. We suggest that any future trial that aims to establish either the benefit of or optimum range of TGC should consider each independently and aim to control hyperglycemia and aggressively avoid hypoglycemia.

Our study had limitations inherent in any retrospective study. Specific to this type of study, which aims to correlate glucose control and outcome, it is impossible to clearly delineate the specific contribution of all the factors that contribute to a patient's glucose control. These include but are not limited to the TGC protocol, the often-changing patient circumstances and physiology, as well as nursing response and behavior, which leads to an insulin dose. Some of these factors will be mitigated by closed-loop glucose measuring and insulin dosing as well as nursing decision support for insulin dosing. An additional consideration is the contribution that brain injury contributes to mortality in critically ill trauma patients. Our logistic regression model was based on the first 72 hours of ICU stay so that all patients were able to contribute to the model. In eliminating this survivor bias, the model still shows that glycemic derangement is predictive of mortality. It may be that traumatic brain injury causes glycemic derangement or vice versa. We cannot discern this from a retrospective study. It is not known whether TGC is of benefit in this population and if so in what range. Likely, patients who are so severely brain injured that they progress to brain death do not benefit from TGC, however, to exclude them from analysis would be to exclude a population who was maintained on a TGC protocol. Further data are necessary to make clear which populations benefit most from TGC.

Our study contributes to the evidence that poor glucose control is associated with mortality. It cannot be determined from retrospective data whether poor glucose control is a marker for poor outcome or a cause of it. Although there have been many proposed measures to show adequate glycemic control, we believe that a standardized variable or set of variables would allow for better comparisons between populations and establish clearly whether TGC does in fact save lives. It also would allow a better understanding of the true cost to save 1 life using a TGC protocol. We believe that calculating both the AUC hyperglycemic and AUC hypoglycemic are important metrics to evaluate a patient's glycemic control as well as the effectiveness of a TGC protocol.

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Discussion

Walter L. Biffl, M.D. (Denver, CO): In surgery and critical care few studies have had such immediate and far-reaching impact on practice as that of Van den Berghe and colleagues[30] in 2001. Based on the results of this single-institution clinical trial, TGC in the range of 80 to 110 g/dL became standard practice in ICUs and, in fact, was endorsed by numerous professional organizations. But there remained some unresolved issues related to the optimal clinical setting, patient population, glucose control regimen, and target glucose level. Based on their findings, the authors have suggested that the method of calculating AUC including both time and glucose measurement is a superior metric to assess glucose control and predict mortality in their patients. In order to put this in context, I have just a couple of questions. First, regarding the patient population, half the patients in this study had traumatic brain injury (TBI), and among the nonsurvivors, over 60% had TBI. Many patients with severe TBI are going to die of that injury regardless of glucose control or any interventions in the ICU. What was the attributable cause of death in the patients who died, and how does it affect your conclusions if you exclude the TBI deaths? Second, it is difficult to maintain perfect glucose control in the range of 80 to 110. Regarding the consequences of less tight glucose control, you point out that multiple small derangements on the hyperglycemic side are not associated with mortality, but you note that any hypoglycemia is detrimental. Consequently, you suggest in your manuscript a more relaxed target of a 100 to 150 and this is supported by recent literature. In fact, I was surprised that in the manuscript you did not discuss the recent NICE SUGAR trial, which threw a bit of cold water on the concept of TGC in the 80 to 110 range. With more relaxed glucose control, you would likely have less hypoglycemia. Given that your study period ended in December of 2007, I was wondering whether you had in fact changed your regimen or if you are still attempting TGC (80–110)? In the end, I think your conclusion is the most valuable take-home lesson: that we need to avoid prolonged high degrees of hyperglycemia and avoid all hypoglycemia.

Michael Corneille, M.D. (San Antonio, TX): With regard to traumatic brain injury, we certainly recognize that, and that is the most common cause for mortality in our ICU and this is why we did a logistic regression model to try to control for brain injury using the admission Glasgow Coma Score to do that. We will certainly have to go back and look at our data to ascertain what was the attributable cause of death in those that did die. With regard to hypoglycemia and hyperglycemia, I believe that they are independent. I think there has been some benefit demonstrated to reducing hyperglycemia, but I think there is also some detriment from hypoglycemia. So I think that they are 2 independent functions and whatever is done to control glycemia in the ICU needs to find the point at which there is maximum benefit from reduction in hyperglycemia and with elimination of

detriment from hypoglycemia. You asked if we changed our protocol. We have not yet because we have not found anyone that showed us what a better one is. There have been many attempts and many different ranges have been published in the literature, but there has been no real scientific effort to find out both what is the best glucose range for patients in the ICU and, secondly, what type of glycemic control protocol gets you there best. So we have not changed our range in our ICU.

Fred Moore, M.D. (Houston, TX): Echoing Dr. Biffl, the Van den Berghe et al[30] trial has had this tremendous impact, but nobody has been able to repeat it. Paul Merritt just did a meta-analysis and there was an important confounding variable. In the Van den Berghe et al[30] trial they started total parenteral nutrition and these patients are getting heavy glucose loads. Now, that could be that insulin with high glucose infusion is actually an anabolic thing, so it could prevent breakdown of muscle, but it also could prevent serious hypoglycemic episodes. And that is the reason everybody is backing away from the 80 to 110 because the incidence of severe hypoglycemia less than 40 is significant, up to 10% of patients. So my questions are 2: what is your practice as far as nutrition in your ICU? Are you giving total parenteral nutrition early? I suspect not. And what is the incidence of severe hypoglycemia in your patients below 40?

Dr Michael Corneille: With regard to nutrition we strongly prefer enteral nutrition to parenteral nutrition. And so, no, it is not a routine that these patients are on total parenteral nutrition for nutrition. We feed as early as we can and prefer an enteral route. Also, I agree with you that it may be, as Van den Berghe et al[30] titled their paper, intensive insulin therapy, that is of benefit; although reduction in hyperglycemia has been shown in several studies to have an association with improvements in morbidity and mortality. With regard to severe hypoglycemia, I will have to go back and quantify, but in our unit, anecdotally, I cannot remember a case of a patient having a seizure or some other untoward consequence of severe hypoglycemia and I think our data show that it is not necessarily severe hypoglycemia, it is really any hypoglycemia. Now, whether that is underlying patient physiology that creates that association or not, that is our protocol. We cannot quite tease that out.