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Finding the sweet spot: Identification of optimal glucose levels in critically injured patients

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Abstract

Background—Conflicting data exist regarding optimal glycemic control in critically ill trauma patients. We therefore compared glucose parameters and outcomes among three different glycemic control regimens in a single trauma ICU, hypothesizing that a moderate regimen would yield optimal avoidance of hyper- and hypoglycemia with equivalent outcomes when compared to a more aggressive approach.

Methods—We retrospectively reviewed 1422 trauma patients with at least 3-day ICU stay and 5 glucose measurements from May 2001 – January 2010, spanning three non-overlapping, sequential glucose control protocols: ‘relaxed’, ‘aggressive’, and ‘moderate’. For each, we extracted mean blood glucose, hypoglycemic and hyperglycemic event frequency, and glucose variability, and investigated their association with outcomes.

Results—Mortality was associated with elevated mean glucose (135.6 vs. 126.2 mg/dL), more frequent hypoglycemic (2.67 ± 7 vs. 1.28 ± 5) and hyperglycemic (30.6 ± 28 vs. 16.0 ± 22 per 100 patient-ICU-days) events, and higher glucose variability (37.1 ± 20 vs. 29.4 ± 20 ; all $p < 0.001$). Regression identified hyperglycemic episodes ($p < 0.05$) as an independent predictor of mortality. The ‘moderate’ regimen had rare hyperglycemia, low glucose variability, and intermediate mean blood glucose range and frequency of hypoglycemia. Multiorgan failure and mortality did not differ between groups.

Conclusions—Hyperglycemic events (glucose > 180 mg/dL) most strongly predicted mortality. Of glucose control protocols analyzed, the ‘moderate’ protocol had fewest hyperglycemic events. As outcomes were otherwise equivalent between ‘moderate’ and ‘aggressive’ protocols, we conclude that hyperglycemia can be safely avoided using a moderate glycemic control protocol without inducing hypoglycemia.

Keywords

Glucose; critical care

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INTRODUCTION

The association of hyperglycemia with morbidity and mortality is well documented in multiple critically ill populations; however, conflicting data exist regarding the efficacy of tight glycemic control in improving outcomes in these patient populations.¹ An early landmark prospective randomized controlled trial of tight glycemic control demonstrated better outcomes in surgical ICU patients with tightly controlled blood glucose;² however, recent studies have suggested that the increase in hypoglycemic events caused by the pursuit of tighter glycemic control regimens may in fact be associated with increased morbidity and mortality.³ The conflicting nature of these disparate data has left optimal glycemic control strategies unclear. Further complicating the issue for the care of the critically ill trauma population is the fact that while these large trials were performed in mixed surgical² and medical/surgical³ populations, the correct balance of glycemic control is understudied in the critically-injured trauma population. These patients tend to be younger and have lower pre-existing incidence of diabetes compared to the patient populations in the above trials, and frequently face unique challenges such as multiple operative interventions and attendant changes in enteral and intravenous nutrition schedules that can cause rapid fluctuations in blood glucose.

Reflecting these differences, a large retrospective study found that hyperglycemia was more strongly correlated with mortality in trauma patients compared to other surgical ICU patients.⁴ Several investigators have demonstrated that admission and early hyperglycemia predicts mortality after trauma; further correlation between early hyperglycemia and infectious morbidity has been demonstrated in some studies,^{5–8} but not others.^{9,10} Preoperative hyperglycemia has also been shown to correlate with poor outcomes in the subset of trauma patients requiring urgent surgical intervention.¹¹ Other trauma-specific studies have investigated the effects of persistent hyperglycemia, and begun to specifically identify patterns of glycemia that are associated with poorer outcomes;^{12–14} however, interpretation of these results is complicated by the use of different thresholds to define hyper- and hypoglycemia. The few studies that have evaluated the influence of glycemic control protocols on outcomes in critically-injured trauma patients have found that a more aggressive protocol decreased overall mean blood glucose levels, but that this decrease was not associated with improved outcomes.^{9,15} In concert with other large trials in the wider literature,³ recognition of the importance of blood glucose variability and the incidence of hyper- and hypoglycemia in addition to the contribution of elevated mean blood glucose to overall outcomes has been recognized as critical.

Clear guidance on the correct glycemic control strategy for trauma patients continues to be inadequate. Over the span of the above-cited reports, the standard glucose control protocol at the San Francisco General Hospital has changed to reflect available evidence. Our purpose was to analyze previous and current glycemic control regimens at our institution in terms of relevant glycemic control parameters, and to evaluate their relative efficacy and outcomes in order to determine an optimal glycemic control strategy.

MATERIALS AND METHODS

We retrospectively reviewed our prospectively-collected bioinformatics database and trauma registry for 2401 adult trauma ICU patients with documented fingerstick blood glucoses from May 2001 – January 2010. Admissions that exceeded 3 ICU days and included more than 5 glucose blood draws were selected for analysis for a total of 1,422 patients with 106,110 total blood glucose measurements. The 9-year study period spanned the sequential, non-overlapping use of three distinct glucose control protocols using continuous IV insulin: ‘relaxed’ from 5/2001 to 5/2005, ‘aggressive’ from 6/2005 to 2/2006, and ‘moderate’ from

3/2006 to 1/2010. All three protocols are standard paper orders, filled out at the discretion of the managing service. The 'relaxed' insulin protocol initiated an IV insulin drip with a fingerstick blood glucose measurement above 180 and targeted blood glucose levels below 180 mg/dL; fingerstick measurements were required every hour until the drip rate was stable for two hours running, when measurements were done every 2 hours. The 'aggressive' protocol initiated an insulin drip for glucose above 120 mg/dL and targeted a blood glucose range of 80–120 mg/dL; measurements were required every hour until within goal range, then continued every other hour. The 'moderate' protocol initiated an insulin drip for glucose ≥ 160 or ≥ 200 mg/dL based on physician-selected check box and targeted a range of 80–140 mg/dL; measurements were required every two hours unless glucose levels or drip rates fell outside of a prespecified range, in which case measurements were taken every hour until glucose levels and drip rate were within range. In all protocols, IV insulin was discontinued and glucose monitored hourly for glucose ≤ 80 mg/dL, and D50 given and the service resident immediately notified for glucose ≤ 60 mg/dL. All protocols also mandated stopping IV insulin infusion immediately when enteral or IV nutrition was held, or when the patient was off-unit for more than 1 hour. Use of an IV insulin drip was identified by insulin administration with dosage recorded as units per hour (as opposed to subcutaneous bolus insulin). Based on previous literature and clinical utility, a hypoglycemic event was defined as a recorded blood glucose of <60 mg/dL and a hyperglycemic event was defined as a recorded blood glucose of >180 mg/dL; each was standardized as events per 100 patient-ICU days.

Baseline and outcome data were obtained for the duration of each patient's ICU admission from multiple sources including ICU electronic flow-sheets (ICU length of stay, duration of mechanical ventilation, fingerstick and serum blood glucose values, inpatient steroid treatment, and IV insulin administration), electronic medical records (age, gender, hospital length of stay, and diagnostic codes) and the institutional trauma registry (injury severity score (ISS), Glasgow coma scale (GCS), and mechanism of injury). Patients whose ICU stay spanned more than one time period were excluded. To standardize the calculation of ICU length of stay, patients who were transferred out of and subsequently readmitted to the ICU were also excluded. Patients were defined as having traumatic brain injury (TBI) if they were identified as traumatically injured by the trauma registry and had an ICD-9 diagnostic code specifying intracranial injury. Pre-existing diabetes was identified by ICD-9 code. Analyses were performed with both diabetic patients included and excluded, and results did not differ; results presented here therefore include all patients identified as having pre-existing diabetes.

For each patient, we extracted mean blood glucose, frequency of hypoglycemic (< 60 mg/dL) and hyperglycemic (> 180 mg/dL) events per 100 patient-ICU-days, and glucose variability (measured as intra-patient standard deviation between all ICU glucose measurements). In order to sensibly interpret glucose variability, patient glucose values were presented as a mean per patient despite a slightly right-skewed distribution; this reflects common practice in the glycemic control literature. Given the non-normal distribution of these data at the cohort level, summary results for each time period are presented as medians and interquartile ranges (IQR) as indicated. Outcome measures were ICU and hospital length of stay, days of mechanical ventilation, multiorgan failure (MOF), and mortality. Multiorgan failure was defined by the Denver score algorithm and was calculated each day until a patient achieved MOF status or reached the 28th day of ICU admission, whichever came first. Mortality was defined as death at discharge.

Statistical analysis was performed using Stata version 11 (StataCorp; College Station, TX), using standard nonparametric univariate statistical methods and linear and logistic regression analysis. Adopting a conservative analysis plan to avoid type I error in comparing

the three defined time periods, specific inter-group comparisons were only made if an overall Kruskal-Wallis (for continuous variables) or Fisher's exact (for dichotomous variables) test reflected significant differences at an alpha of 0.05; this was followed by specific inter-group comparisons using Mann-Whitney (for continuous variables) and Fisher's exact (for dichotomous) tests and a Bonferroni-adjusted alpha of 0.0167 as noted.

RESULTS

Baseline characteristics of our aggregate study population are presented in Table 1; patient characteristics by glycemic control protocol and time period are presented in Table 2. The three populations had similar age, body mass index (BMI), ISS, percentage of blunt injury, and percentage of TBI. Admission GCS was statistically lower in the 'relaxed' (10.9, IQR 7–15) compared to the 'aggressive' (12.2, IQR 11–15) and 'moderate' time periods (11.8, IQR 10–15; Kruskal-Wallis $p < 0.001$), although this is of doubtful clinical significance. As initiation of the glucose control protocol was at the discretion of the managing service, the percentage of patients on IV insulin during each time period differed significantly: drip use corresponded to the aggressiveness of the glucose target for each time period, spanning from 24.7% in the 'relaxed' group to 56.7% in the 'aggressive' group, with an intermediate 38.7% on drip in the 'moderate' group (all Fisher's exact $p < 0.001$). Steroid use showed a trend for statistical difference between time periods (overall Fisher's exact $p = 0.042$) with the highest rate of use during the 'relaxed' time period (16.7%) and lowest during the 'aggressive' time period (10.0%); however, using a Bonferroni-corrected alpha, there were no significant differences between individual time periods (all inter-group Fisher's exact $p < 0.0167$).

Characteristic glycemic control parameters for each glycemic control protocol and time period are presented in Table 3. Mean blood glucose levels differed significantly between time periods: the highest mean blood glucose level was observed in the 'relaxed' time period (133, IQR 121–149), the lowest in the 'aggressive' time period (121, IQR 114–132), and an intermediate level in the 'moderate' time period (126, IQR 119–137; Kruskal-Wallis $p < 0.001$; all Mann-Whitney $p < 0.001$). Blood glucose variability (assessed as the standard deviation of all blood glucose measurements per each patient) was lowest in the 'moderate' regimen (25.2, IQR 19–35) and differed significantly from the 'relaxed' regimen (27.1, IQR 19–39; Kruskal-Wallis $p = 0.01$; Mann-Whitney $p = 0.0125$), while variability during the 'aggressive' regimen was statistically similar to the other two. Intuitively, hypoglycemic (glucose < 60 mg/dL) events were most common during the 'aggressive' (3.76 ± 10.0) regimen, intermediate during the 'moderate' regimen (1.45 ± 5.1), and lowest during the 'relaxed' (0.77 ± 3.8) regimen (Kruskal-Wallis $p < 0.001$, all Mann-Whitney $p < 0.01$). The percentage of patients in each time period who experienced a hypoglycemic event was 7.6%, 24%, and 12.4% in the 'relaxed', 'aggressive', and 'moderate' regimens, respectively. Hyperglycemic (glucose > 180 mg/dL) events were statistically most common during the 'relaxed' regimen (21.1 ± 25.9) and rarest during the 'moderate' regimen (16.4 ± 21.7 ; Kruskal-Wallis $p = 0.028$; Mann-Whitney $p = 0.007$); interestingly, the 'aggressive' regimen (17.8 ± 24.0) had an intermediate frequency of hyperglycemic events that did not differ significantly from the 'moderate' (Mann-Whitney $p = 0.488$) or 'relaxed' (Mann-Whitney $p = 0.308$) regimen. The percentage of patients experiencing a hyperglycemic event was 63.6%, 64.0%, and 59.5% in the 'relaxed', 'aggressive', and 'moderate' regimens, respectively.

Outcomes by glycemic control regimen and time period are also presented in Table 3. Intensive care unit length of stay was longest during the 'relaxed' regimen (9, IQR 5–18) and shortest during the 'aggressive' regimen (7, IQR 4–12; Kruskal-Wallis $p = 0.01$; Mann-Whitney $p = 0.002$); however, the ICU length of stay during the 'moderate' time period did not differ statistically between the 'aggressive' and 'relaxed' regimens (7, IQR 5–17; Mann-

Whitney $p = 0.0229$ and 0.1497 , respectively; not significant when adjusted for multiple comparisons). Total hospital length of stay differed between groups with the longest median stay in the 'moderate' time period (17, IQR 8–33) and the shortest in the 'aggressive' time period (12, IQR 6–29), but when corrected for multiple comparisons, these differences were not significant (Kruskal-Wallis $p = 0.044$; but all Mann-Whitney $p > 0.0167$). Total ventilator days were significantly highest in the 'relaxed' regimen (5, IQR 2–13; Kruskal-Wallis $p = 0.002$; both Mann-Whitney $p < 0.003$), compared to the statistically similar 'aggressive' (3, IQR 1–9) and 'moderate' regimen (4, IQR 1–14; Mann-Whitney $p = 0.5061$ for 'aggressive' vs. 'moderate'). The incidence of both multiorgan failure and mortality did not differ between any regimen (Fisher's exact $p = 0.196$ and 0.102 , respectively).

In order to determine the relative importance of mean blood glucose, glucose variability, and hypo- and hyperglycemic events to overall outcomes, we next assessed these parameters in our aggregate population including all time periods. Patients who developed multiorgan failure (MOF) had significantly higher glucose variability (33.58 ± 18.1 vs. 29.3 ± 21.0 ; $p < 0.0001$), more common hypoglycemic events (1.84 ± 5.1 vs. 1.35 ± 5.7 ; $p < 0.0001$), and more common hyperglycemic events (22.1 ± 24.2 vs. 16.6 ± 23.0 ; $p < 0.0001$) than those who did not; mean blood glucose did not differ (126.3 , IQR 119–140 vs. 127.6 , IQR 117–140; $p = 0.3439$; see Figure 1). Using logistic regression analysis to adjust for the contribution of other factors, BMI, ISS, GCS, steroid use, tube feeding, and IV insulin use were found to be significant independent predictors of MOF (all $p \leq 0.01$; see Table 4), likely as surrogates for clinical severity and prolonged ICU stay. None of the four glycemic control parameters analyzed independently predicted MOF. Similar analysis was carried out to identify factors associated with mortality. Patients who died in-hospital had significantly higher mean blood glucose (135.6 , IQR 124–148 vs. 126.2 , IQR 117–139; $p < 0.0001$) and glucose variability (37.1 ± 20.3 vs. 29.4 ± 20.1 ; $p < 0.0001$), as well as more common hypo- and hyperglycemic events (2.68 ± 7.0 and 30.6 ± 27.6 vs. 1.28 ± 5.2 and 16.0 ± 22.0 ; $p < 0.0002$ for both) than those who survived to discharge (see Figure 2). When logistic regression was used to adjust for other factors, hyperglycemic events were found to be a significant predictor of mortality (odds ratio 4.82; $p = 0.035$), as were age, ISS, GCS, and TBI (all $p < 0.005$; see Table 5).

DISCUSSION

Given conflicting data regarding optimal glycemic control in critically-injured trauma patients, we sought to describe previous and current existing glycemic control regimens at our institution in terms of relevant glycemic control parameters, and to evaluate their relative efficacy and outcomes. Here we describe characteristic mean blood glucose, glucose variability, and incidence of hypo- and hyperglycemia under three distinct regimens used during non-overlapping time periods. Overall, our 'relaxed' regimen had high mean glucose, intermediate glucose variability, rare hypoglycemia, and common hyperglycemia; the 'aggressive' regimen had low mean glucose, more common hypoglycemia, and uncommon hyperglycemia; and the 'moderate' regimen had intermediate mean blood glucose and hypoglycemic frequency, but the least glucose variability and rarest incidence of hyperglycemia. In terms of outcomes, the 'moderate' protocol had total ICU, hospital, and ventilator days statistically similar to or shorter than the other two regimens, with no statistical difference between incidence of multiorgan failure or mortality between any of the three groups. Using regression analysis in the aggregate population across all groups, frequency of hyperglycemic events was found to be the only glycemic control parameter that was independently associated with mortality. Taken together, these data suggest that, between the three strategies compared, a 'moderate' glycemic control regimen provides the most optimal combination of glycemic control consisting of primary avoidance of

hyperglycemia, tempered with low glucose variability, moderate normoglycemic targeting, and reductions in hypoglycemia.

The literature describing the importance of glycemic control to outcomes after trauma is populous and complex. Large prospective, randomized controlled trials including few trauma patients had originally suggested conflicting priorities for glycemic control in the ICU, with an early study emphasizing tight glycemic control² as critical for reducing morbidity and mortality, but a subsequent multicenter trial suggesting that the increased frequency of hypoglycemia in the setting of tight glycemic control in fact contributes to *increased* morbidity and mortality.³ In an effort to parse this conflicting data, several investigators have highlighted the relatively stronger correlation between early hyperglycemia and poor outcomes in trauma patients compared to other critically ill surgical patients.⁴ Our results support this focus on avoidance of hyperglycemia: of the four glycemic control parameters described, only hyperglycemia was independently associated with increased mortality in our regression analysis. However, knowledge of the association between hyperglycemia and poor outcomes after trauma does little for the clinician at the ICU bedside, as aggressive insulin therapy may also be deleterious as has been demonstrated in the broader critical care literature.^{3,16,17} To address this concern in a practical sense, our study attempts to identify which of three preexisting glycemic control regimens at our institution best prevents hyperglycemia while simultaneously avoiding an over-exuberant pursuit of normoglycemia that may lead to potentially dangerous hypoglycemia.

As demonstrated, our 'moderate' protocol appears to best accomplish these criteria by avoiding hyperglycemic events while providing satisfactory overall glucose control, with outcomes equivalent or superior to a preceding 'aggressive' protocol. In fact, the 'moderate' protocol was developed in response to staff and nursing concerns raised regarding the burdensome frequency of blood glucose checks (hourly during periods of changes in the drip dosing in response to out-of-range glucose levels) required by the 'aggressive' protocol as well as the anecdotal concern that hypoglycemic events were significantly more common during the 'aggressive' regimen. As noted by several authors, the difficulty of adequately achieving very low target glycemic ranges as well as the difficulty of implementing these protocols from a workflow point of view may make more stringent glycemic control protocols untenable in a busy trauma ICU.^{15,18}

Although multiple studies exist describing the association of hyperglycemia to outcomes after trauma, few studies undertaken in trauma populations compare the effect of different glycemic control protocols on outcomes. Wahl *et al.*⁹ presented a historically-controlled study of outcomes before and after institution of a mandatory insulin infusion protocol for mechanically-ventilated trauma patients with blood glucose levels > 140 mg/dL. Similar to our findings, institution of a more aggressive glycemic control protocol reduced mean blood glucose values and increased the incidence of hypoglycemic events, but did not significantly improve outcomes. This study included all 531 patients admitted to the trauma ICU during the study period, and did not exclude patients with single glucose values or single-day ICU stays. These criteria may account for differences in the percentage of patients receiving continuous IV insulin, which in the Wahl study was 13% in historical controls and 22% under the more aggressive regimen, compared to 24.7% of patients in the 'relaxed', 56.7% in the 'aggressive', and 38.7% in the 'moderate' regimen in our study. Similarly, Collier *et al.*¹⁵ compared outcomes before and after institution of a glycemic control protocol targeting blood glucose < 110 mg/dL in 818 patients. Again outcomes were equivalent between groups, and hyperglycemia was shown to correlate with increased mortality; however, mean blood glucose was not significantly lower after institution of the more aggressive glycemic control protocol (130.5 ± 11.2 vs. 124 ± 12.8 mg/dL; $p = 0.168$), and neither group achieved target glucose levels of 80–110 mg/dL for the study period. Our study supports and extends

the results of this prior work by examining a broader study population and evaluating the relative utility of three separate glycemic control protocols, providing greater generalizability. Additional rigorous studies would be needed in order to identify the specific normoglycemic ranges and protocol adjustment and monitoring characteristics required to achieve target glucose levels. However, by comparing the actual mean glucose level achieved under these three protocols, our analysis avoids comparing target ranges that may or may not be met in individual patients and presents a more easily generalized, intention-to-treat analysis.

The limitations of this study clearly include its single-institution retrospective nature, as well as the variability in individual attending trauma surgeons' practice in terms of glycemic control strategies. The lack of criteria for mandatory initiation of the standardized time period-specific IV insulin drip protocol makes comparison between time periods prone to type II error. In particular, by including patients with out-of-target-range glucose values that may not have been placed on the standardized insulin drip in each time period, differences in glycemia between those patients on an insulin drip may be obscured; the reduction in the resolution between individual time periods may mask true significant differences in morbidity and mortality. This may be particularly true of the 'relaxed' regimen, as this time period from 2001 until 2005 co-occurred with the publication of key studies that had a significant impact on the clinical management of hyperglycemia.^{2,5-7} All of these factors may contribute to insufficient resolution to detect subtle differences; this may be the case in identifying predictors of multiorgan failure, in which wide confidence intervals were seen in the estimated odds ratios for hypo- and hyperglycemic event frequency which did not exclude the possibility of a clinically meaningful effect (see Table 4). However, the finding that hyperglycemia was a clear statistically significant predictor of overall mortality indicates sufficient power of this study to detect critical differences in outcome based on glycemic control parameters. Overall, we find that including both patients on and off of continuous IV insulin better reflects the reality of attending-to-attending practice variability common in most trauma ICUs, and increases the external validity of the current study. While these uncertainties could be avoided by randomization and prospective head-to-head evaluation of these three distinct protocols, we suggest that the value of this study lies instead in demonstrating that the balance between overly aggressive and overly relaxed glycemic control can be struck using a feasible, moderate protocol as ongoing study continually refines best practices.

The time resolution of individual glucose measurements for each patient did not permit a more specific analysis of the events surrounding incidences of hyper- and hypoglycemia in this study. However, in concert with other elegant studies addressing specific patterns of glycemic control over time and their contribution to outcomes,^{10,13,14,19,20} we would hypothesize that trauma patients are at relatively increased risk for large fluctuations in blood glucose due to both scheduled and unanticipated interruptions in enteral and parenteral nutrition. Further study will hopefully lead to a more nuanced understanding of both predisposing factors and underlying mechanisms for hypo- and hyperglycemic events, thereby providing a better clinical understanding of their importance and helping to develop optimal peri-procedural protocols.

In summary, in a retrospective review of our institutional experience spanning three distinct glycemic control regimens, we identify hyperglycemia as a significant predictor of mortality in critically-injured trauma patients. Of the three protocols assessed, the 'moderate' glycemic control regimen most optimally balances maintenance of normoglycemia, reduction in glucose variability, and minimization of hypo- and hyperglycemic events, while maintaining equivalent outcomes when compared to a more aggressive strategy.

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Figure 1. Glycemic parameters by patient multiorgan failure

Box-whisker plots demonstrating mean blood glucose (a), glucose variability (b), and incidence of hypoglycemia (c) and hyperglycemia (d) per 100 patient-ICU-days by patients with and without multiorgan failure. Significance by Mann-Whitney ranksum testing with $p < 0.05$ is denoted by an asterisk.

Figure 2. Glycemic parameters by patient mortality

Box-whisker plots demonstrating mean blood glucose (a), glucose variability (b), and incidence of hypoglycemia (c) and hyperglycemia (d) per 100 patient-ICU-days by patients who died versus those who survived. Significance by Mann-Whitney ranksum testing with $p < 0.05$ is denoted by an asterisk.

Table 1

Study Population Characteristics

Age	45 (29–61)
BMI	27.5 ± 5.8
% Male	74.1%
ISS	26 (17–34)
GCS	14 (9–15)
% Blunt	77.0%
% TBI	52.2%

Data are presented as median (interquartile range) or mean ± standard deviation. BMI = body mass index, ISS = injury severity score, GCS = Glasgow coma score, TBI = traumatic brain injury.

Table 2

Study Population Characteristics by Timeframe

	RELAXED (n = 450)	AGGRESSIVE (n = 150)	MODERATE (n = 822)	p-value
Glucose target	<180	80–120	80–140	
Age	38.3 (30–46)	48.1 (31–62)	47.3 (29–61)	0.136
BMI	27.1 ± 5.7	27.5 ± 5.4	27.6 ± 5.9	0.710
ISS	25.9 (17–33)	27.0 (17–34)	26.7 (17–34)	0.553
GCS	10.9 (7–15) [‡]	12.2 (11–15)	11.8 (10–15)	0.001 [*]
% Blunt	76.2%	79.3%	77.0%	0.748
% TBI	55.1%	50.7%	50.9%	0.328
% Steroid use	16.7%	10.0%	12.3%	0.042 [*]
% Tube fed	26.7%	24.0%	21.2%	0.084
% IV insulin	24.7% [‡]	56.7% [‡]	38.7% [‡]	0.001 [*]

Data are presented as median (interquartile range) or mean ± standard deviation. BMI = body mass index, ISS = injury severity score, GCS = Glasgow coma score, TBI = traumatic brain injury.

* p < 0.05 by Kruskal-Wallis or Fisher's exact testing

[‡] Indicated time periods differ significantly from each other

[‡] Indicated time period differs significantly from other two

Table 3

Glycemic Control by Regimen

	RELAXED (n = 450)	AGGRESSIVE (n = 150)	MODERATE (n = 822)	p-value
Glucose target	<180	80–120	80–140	
% IV insulin use	24.7% [†]	56.7% [†]	38.7% [†]	0.001 *
Mean blood glucose	133 (121–149) [†]	121 (114–132) [†]	126 (119–137) [†]	0.001 *
Glucose variability	27.1 (19–39) [†]	28.0 (20–38)	25.2 (19–35) [†]	0.010 *
Hypoglycemia/100pt-d	0.77 ± 3.8 [†]	3.76 ± 10.0 [†]	1.45 ± 5.1 [†]	0.001 *
Hyperglycemia/100pt-d	21.1 ± 25.9 [†]	17.8 ± 24.0	16.4 ± 21.7 [†]	0.028 *
ICU days	9 (5–18) [†]	7 (4–12) [†]	7 (5–17)	0.010 *
Hospital days	16 (8–30)	12 (6–29)	17 (8–33)	0.044 *
Ventilator days	5 (2–13) [‡]	3 (1–9)	4 (1–14)	0.002 *
Multiorgan failure	29.1%	22.0%	25.8%	0.196
Mortality	16.9%	14.7%	12.5%	0.102

Data are presented as median (interquartile range) or mean ± standard deviation.

* p < 0.05 by Kruskal-Wallis or Fisher's exact testing

[†] Indicated time periods differ significantly from each other

[‡] Indicated time period differs significantly from other two

Table 4

Multivariate Predictors of MOF

	Odds ratio	SE	p-value	95% CI
Mean blood glucose	0.987	0.007	0.104	0.975 – 1.002
Glucose variability	1.008	0.005	0.089	0.999 – 1.017
Hypoglycemia/100pt-d	1.474	2.448	0.815	0.057 – 38.18
Hyperglycemia/100pt-d	0.585	0.366	0.392	0.172 – 1.996
Age	1.006	0.005	0.254	0.996 – 1.015
BMI	1.041	0.016	0.008*	1.011 – 1.072
ISS	1.029	0.007	<0.001*	1.016 – 1.042
GCS	0.947	0.020	0.009*	0.909 – 0.987
TBI	0.881	0.180	0.535	0.590 – 1.315
Steroid use	2.543	0.687	0.001*	1.498 – 4.317
Blunt mechanism	1.447	0.351	0.128	0.899 – 2.330
Tube feeding	1.954	0.369	<0.001*	1.350 – 2.828
IV insulin use	2.094	0.423	<0.001*	1.409 – 3.112

Logistic regression analysis of predictors of multiorgan failure. BMI = body mass index, ISS = injury severity score, GCS = Glasgow coma score, TBI = traumatic brain injury, SE = standard error, CI = confidence interval.

Table 5**Multivariate Predictors of Mortality**

	Odds ratio	SE	p-value	95% CI
Mean blood glucose	0.999	0.008	0.824	0.982 – 1.014
Glucose variability	1.006	0.007	0.404	0.992 – 1.019
Hypoglycemia/100pt-d	0.776	1.435	0.891	0.021 – 29.04
Hyperglycemia/100pt-d	4.823	3.607	0.035*	1.113 – 20.89
Age	1.050	0.007	<0.001*	1.036 – 1.065
BMI	1.012	0.022	0.587	0.970 – 1.056
ISS	1.030	0.009	0.001*	1.013 – 1.047
GCS	0.884	0.025	<0.001*	0.837 – 0.934
TBI	2.438	0.736	0.003*	1.349 – 4.405
Steroid use	1.087	0.411	0.825	0.509 – 1.411
Blunt mechanism	0.774	0.309	0.521	0.354 – 1.693
Tube feeding	0.847	0.220	0.524	0.509 – 1.411
IV insulin use	1.300	0.380	0.377	0.729 – 2.303

Logistic regression analysis of predictors of mortality. BMI = body mass index, ISS = injury severity score, GCS = Glasgow coma score, TBI = traumatic brain injury, SE = standard error, CI = confidence interval.