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Software-Guided Insulin Dosing: Tight Glycemic Control and Decreased Glycemic Derangements in Critically Ill Patients

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Abstract

Objective: To determine whether glycemic derangements are more effectively controlled using software-guided insulin dosing compared with paper-based protocols.

Patients and Methods: We prospectively evaluated consecutive critically ill patients treated in a tertiary hospital surgical intensive care unit (ICU) between January 1 and June 30, 2008, and between January 1 and September 30, 2009. Paper-based protocol insulin dosing was evaluated as a baseline during the first period, followed by software-guided insulin dosing in the second period. We compared glycemic metrics related to hyperglycemia, hypoglycemia, and glycemic variability during the 2 periods.

Results: We treated 110 patients by the paper-based protocol and 87 by the software-guided protocol during the before and after periods, respectively. The mean ICU admission blood glucose (BG) level was higher in patients receiving software-guided intensive insulin than for those receiving paper-based intensive insulin (181 vs 156 mg/dL; P=.003, mean of the per-patient mean). Patients treated with software-guided intensive insulin had lower mean BG levels (117 vs 135 mg/dL; P=.0008), sustained greater time in the desired BG target range (95-135 mg/dL; 68% vs 52%; P=.0001), had less frequent hypoglycemia (percentage of time BG level was <70 mg/dL: 0.51% vs 1.44%; P=.04), and showed decreased glycemic variability (BG level per-patient standard deviation from the mean: ±29 vs ±42 mg/dL; P=.01).

Conclusion: Surgical ICU patients whose intensive insulin infusions were managed using the software-guided program achieved tighter glycemic control and fewer glycemic derangements than those managed with the paper-based insulin dosing regimen.

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Glycemic control has become an increasingly important element of care in critically ill patients secondary to the discovery that severe stress hyperglycemia is strongly associated with increased mortality.[1,2] Clinical outcomes were improved in single-center studies spearheaded by Van den Berghe et al[3-5] in which intensive insulin therapy using standardized methods of blood glucose (BG) measurement and insulin dosing calculation had been applied rigorously and consistently in practice for many years. Current debate in this field centers on the appropriate target range for optimal glycemic control[6]; the consequences of iatrogenic hypoglycemia, whether mild or severe[7,8]; the emerging appreciation for the effect on patient outcome conferred by glycemic variability (GV)[9-12]; and the realization that the safe and effective use of intensive insulin requires frequent measurement of BG levels, which is labor intensive.[13] A newly published study showed that the 3 domains of glycemic control (ie, hyperglycemia, hypoglycemia, and GV) are altered on the basis of whether the patients have diabetes. In this cohort, GV was associated with an increased risk of mortality only in nondiabetic patients.[14]

Several large, prospective, randomized multicenter trials[15-17] failed to confirm that "tight" glycemic control applied in the manner of Van den Berghe (BG target range of 80-110 mg/dL [to convert to mmol/L, multiply by 0.0555]) decreased mortality rates. However, it has since been determined that these studies had a significant proportion of protocol violations and methodological flaws.[6] These studies were

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conducted using a combination of imperfect techniques that may be practical but when used together undermine the goal of achieving safe, tight control of BG levels as advocated by Van den Berghe.[6,18,19] For example, heavy dependence on generic paper-based protocols to estimate insulin dosing as a "one size fits all" approach is a practice that challenges nursing compliance.[20-22] It may also be that simply achieving a mean BG level in the target range without BG stability is a flawed goal for intensive insulin therapy.

It is well established that hypoglycemia is strongly associated with mortality in critically ill patients.[23-25] Glycemic variability is now also recognized as a predictor of death, independent of hypoglycemia and the mean BG level. Finney et al[26] first observed that intensive care unit (ICU) patients commonly experienced wide fluctuations in BG levels despite close monitoring and the use of standardized intensive insulin infusions. Egi et al[27] identified a relationship between the standard deviation from the mean BG level and hospital mortality in the ICU. Subsequent studies have uniformly confirmed this early finding,[9,10,28-31] and it has been reported that the adjusted odds of death associated with GV are greater than with hypoglycemia alone.[32] To date, there are no published studies examining how to best control and mitigate GV, which is now believed to be a dynamic surrogate of glycemic dysregulation and a predictor of death.[9,10,27-31] Glycemic variability has been defined using an assortment of metrics, including the standard deviation from the mean BG level,[27] the coefficient of variation (CV),[33,34] the glycemic penalty index (GPI),[35] and the mean amplitude of glycemic excursions (MAGE).[36]

Several reports of software-guided insulin dosing have shown improved glycemic control while lowering hypoglycemia rates.[37-39] We hypothesized that software-guided insulin dosing would be superior to paper-based protocols not only in increasing the time of BG in the target range but also in controlling GV as a means to achieve safe, tight glycemic control. To test this hypothesis, we compared 2 periods of intensive insulin management in a pilot trial of critically ill surgical patients: a baseline period during which insulin dosing was based on a paper protocol and a follow-up comparison period after transitioning to a software-guided system.

PATIENTS AND METHODS

Setting and Study Population

The Tufts Medical Center (Boston, Massachusetts) surgical ICU is a 10-bed unit that accepts all noncardiac surgical patients, including those undergoing general and vascular, otorhinolaryngologic, orthopedic, neurologic, trauma, thoracic, high-risk obstetric, and oncologic surgery. It is a teaching unit managed by a multidisciplinary team.

Glucose Control Practice

Intensive insulin therapy was implemented by ICU policy in 1998 as a continuous infusion targeting a BG level less than 180 mg/dL. The current targeted BG range in the surgical ICU (95-135 mg/dL) was established using a paper-based protocol in 2002. By 2008, the experienced nursing staff used the paper-based insulin dosing protocol to maintain BG levels within the target range.[40] In July 2008, we introduced the GlucoStabilizer insulin dosing system (Alere Informatics Solutions) to target the same BG levels.

On admission to the surgical ICU, critically ill patients were started on the paper-based protocol or the GlucoStabilizer as described previously herein if 2 BG measurements were greater than 135 mg/dL. If the patient did not meet the criteria for intensive insulin treatment, he or she was treated with conventional sliding-scale insulin dosing as needed, with the dosing determined by the individual physicians for a preferred BG target range of 95 to 135 mg/dL.

Blood samples for glucose measurement were collected preferentially from arterial sources, which is standard protocol in the surgical ICU. If arterial access was not available, then central venous catheters were accessed for laboratory measurements. Capillary sampling by fingerstick constitutes less than 10% of all samples in the ICU. The BG data were derived from bedside point-of-care meters (ACCU-CHEK Inform; Roche Diagnostics) and were downloaded to the Remote Automated Laboratory System-Plus (RALS-Plus; Alere Informatics Solutions), a laboratory information management system.[41] The meters were calibrated daily. Protocolized care delivery beyond glucose management for both groups did not change between the 2 periods

and was not different between the groups. Nutrition therapy was initiated on the basis of patient clinical need per standardized protocol in both groups and was not included as a factor in this analysis.

Measurements of BG by the paper-based protocol were customarily performed every hour until the BG level was consistently in the desired range; subsequent BG measurements occurred every 2 to 4 hours on the basis of conventional nursing judgment. In the software-guided group, the software determined the timing of BG measurement by programming set to clinician specifications, which for this study period was the same as for the paper-based protocol. The program calculates the next insulin dose and also instructs the nurse as to when the next blood sample should be collected. The practice is for the nurse to administer the software-recommended dose of insulin by infusion; however, should the nurse have reservations regarding the BG measure, he or she is encouraged to repeat the BG measurement and submit the result for inclusion in the recalculation performed by the software. In addition, clinical judgment is to be used before proceeding with any insulin dose adjustment recommended by the software.

Data Abstraction

All surgical ICU patients are prospectively entered into the ICU database (Project IMPACT, Cerner Corp; ICUTracker, Alere Informatics Solutions), which has been used since 1997. We retrospectively analyzed the data collected during 2 distinct periods. The baseline study interval spanned January 1 through June 30, 2008, during which a paper-based insulin titration method for managing intensive insulin therapy was used. The second study period followed the introduction of software-guided insulin dosing in July 2008; patients admitted during a 6-month "run-in" period for nursing education and program implementation were not included in this analysis. January 1 through September 30, 2009, represented the intervention period to study the effects of the software.

Of 236 and 411 admissions during the paper-based and software-guided insulin dosing periods, respectively, 126 and 324 patients were excluded from this study because they did not require continuous insulin infusion for hyperglycemia, defined as a BG level greater than 135 mg/dL on 2 consecutive measurements; did not have at least 3 BG measurements; or received care in the ICU for less than 3 days (Figure 1). In addition, patients were excluded from the study if their care was not managed by the surgical ICU team. Patients were not excluded on the basis of medical diagnosis, complications, or treatments (corticosteroids, enteral nutrition) that are known to predispose patients to hyperglycemia. Subcutaneous insulin was not used in these patient cohorts until the day of discharge from the ICU, when patients were transitioned per protocol from intensive insulin therapy.

We obtained patient demographic characteristics (age and sex) on admission to the ICU. Severity of illness was assessed using the Acute Physiology and Chronic Health Evaluation II (APACHE II) score.[42] The APACHE II scores were dichotomized for lower (<20) and higher (≥20) illness severity on ICU admission for comparison of GV by severity. Markers of glycemic control were defined as hyperglycemia (BG level >135 mg/dL), severe hyperglycemia (BG level >180 mg/dL), hypoglycemia (BG level <70 mg/dL), and severe hypoglycemia (BG level <40 mg/dL).

The presence of preexisting diabetes and sepsis, as defined by *International Classification of Diseases, Ninth Revision* code, and mortality were recorded prospectively. Sepsis was defined as occurring at any time during the ICU stay. Outcome data, including ICU length of stay, number of ventilation days, and ICU mortality, were collected. However, the sample size in this pilot trial was too small to determine a difference in outcome data between patients managed by the 2 methods.

The Human Investigation Review Committee of Tufts Medical Center reviewed and approved the paper vs software comparison design; the study was exempted from informed consent because data were deidentified and analyzed retrospectively.

Glucose Metrics

We analyzed time to target, interval between glucose measurements, percentage of time in the target range (95-135 mg/dL), hyperglycemia (>135 mg/dL), severe hyperglycemia (BG level >180 mg/dL), hypoglycemia (<70 mg/dL), and severe hypoglycemia (<40 mg/dL) in the 2 groups. We also determined the percentage

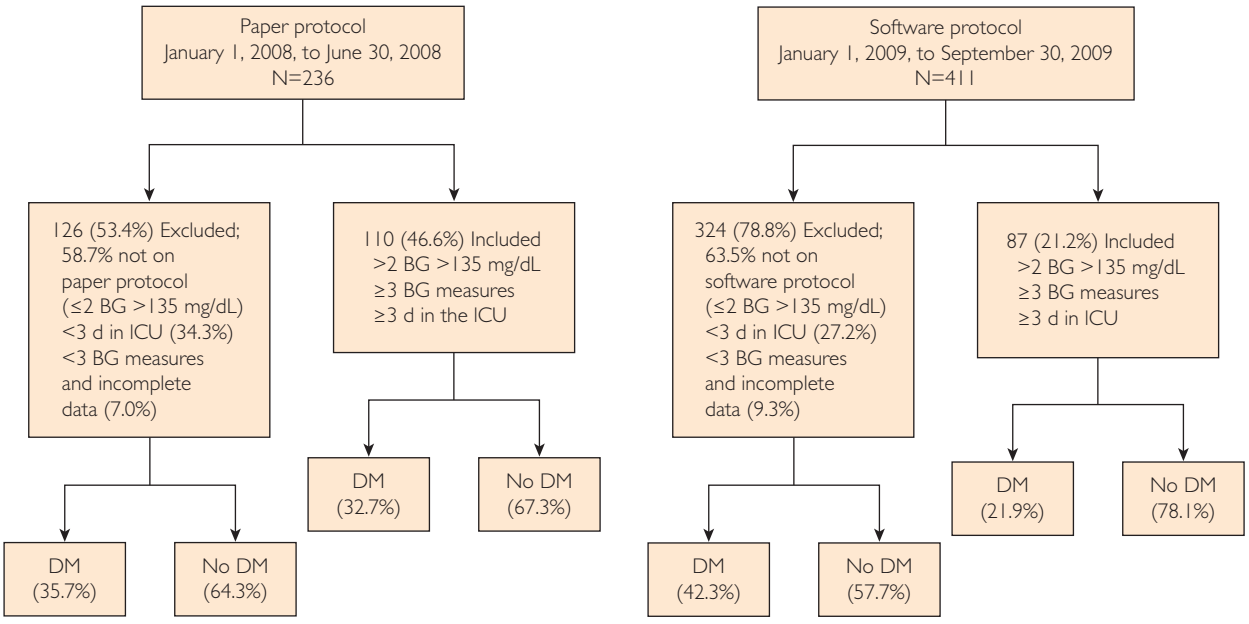

FIGURE 1. Consort chart detailing the study inclusion and exclusion criteria. Patients were stratified by insulin dosing method (paper-based protocol vs software-guided protocol) and by diabetes mellitus (DM) status. BG = blood glucose; ICU = intensive care unit.

of patients with 1 BG measure greater than 135 mg/dL, greater than 180 mg/dL, less than 70 mg/dL, and less than 40 mg/dL for comparison. Variability in BG measures was quantified using 4 different measurements: the standard deviation from the mean[27]; the CV, calculated as standard deviation of the mean glucose level[34]; the GPI, which assigns a progressive penalty for more numerous and longer-duration excursions outside the target range[35]; and the MAGE, which is the average of all BG level increases or decreases that are greater than 1 SD from the mean of all BG measures.[36] The BG variability indices were calculated for the individual patients to derive the cohort mean ± SD.

GlucoStabilizer

The GlucoStabilizer is a computerized intravenous insulin dosing software system that calculates insulin infusion rates for hospitalized patients with hyperglycemia.[37] In brief, when the patient's BG value is entered, the GlucoStabilizer calculates the initial insulin infusion rate in units per hour using (BG − 60) × multiplier, set at an initial default of 0.02. Target range, testing interval, and critical alarms for hypoglycemic BG parameters are based on individual patient requirements and are programmed into the software. The GlucoStabilizer then schedules the next BG measurement (1-2 hours), at which time the program sounds an alarm, alerting the nurse to measure the patient's BG level. When a new BG value is entered, the program recalculates the multiplier, recommends a new insulin infusion rate, and schedules the next measurement. For any BG level of 70 mg/dL or less, the program enters hypoglycemia recovery mode by recommending that the insulin drip be stopped and a 50% dextrose intravenous bolus be delivered, determined by the calculation (100 − BG) × 0.4 mL. After hypoglycemia, the program schedules the next BG measurement for 15 minutes later. Normal mode resumes when the BG level exceeds 70 mg/dL. All drip runs (the per-patient series of calculations and insulin doses) are electronically saved in the GlucoStabilizer database.

Statistical Analyses

Descriptive data are expressed as mean ± SD. For this analysis, consecutive BG measurements were evaluated, regardless of intermittent testing and variable intervals between measurements, with the assumption that a linear relationship existed among measures.

TABLE 1. Baseline Characteristics and Clinical Outcomes of the 2 Groups[a,b]

Characteristic	Paper-based group (n=110)	Software-guided group (n=87)	*P* value
Age (y)	59±14	60±18	.19
Sex, M/F (No.)	56/54	53/34	.07
APACHE II score	16±6	15±6	.42
Diabetes (%)[c]	32.7	22.0	.07
ICU days	6.3±8.6	5.7±8.3	.63
Median	3.1	2.9	
Q1	1.8	1.5	
Q3	6.8	4.7	
Range	0.6-53	0.3-52	
Ventilation (%)	65.5	60.0	.41
Ventilation days	4±8	5±9	.26
Median	1.9	0.9	
Q1	0.7	0.7	
Q3	7.1	4.7	
Range	0.1-53	0.1-52	
ICU sepsis (%)[c]	35.5	24.1	.29
ICU mortality (%)	12	9	.29

[a]APACHE II = Acute Physiology and Chronic Health Evaluation II; ICU = intensive care unit.
[b]Values are presented as mean ± SD unless indicated otherwise.
[c]Defined by *International Classification of Diseases, Ninth Revision* code.

Comparisons between the 2 cohorts included BG measures on ICU admission, during the ICU stay, and at ICU discharge. We made comparisons between the groups using χ^2 and *t* tests, with $P<.05$ (2-sided) considered significant for all the analyses. We performed subgroup analyses of GV in patients with diabetes vs without diabetes using multivariable regression to determine a difference in glucose control in patients with and without diabetes. The multivariable regression model included the following terms: *protocol*, *age*, *sex*, *diabetes status*, and *APACHE II score*. All the terms were included in the model regardless of their *P* values. The study was not powered to assess differences in mortality rates between the 2 groups.

RESULTS

The paper-based protocol cohort included 110 patients, and 87 patients were managed by the software. Complete data were obtained for the entire cohort of 197 patients. Table 1 details the baseline characteristics and selected clinical outcomes of the 2 cohorts. There were no statistically significant differences in the population demographic characteristics or in severity of illness; however, fewer patients in the software-guided group had diabetes.

Table 2 displays the glycemic metrics of the 2 groups. Although patients receiving intensive insulin on the basis of software-guided dosing had a higher mean BG level at the time of insulin initiation ($P=.003$), they were discharged from the surgical ICU more often with a normalized BG level compared with patients managed with the paper-based insulin dosing regimen ($P<.001$). There was a slightly more than 2-fold increase in the number of BG measurements per patient per day in the software-guided group ($P<.001$). Time to target was not statistically significantly different in the 2 treatment groups. Several outliers, patients who were difficult to manage in the paper-based protocol group, contributed to a large deviation from the mean. Control of hyperglycemia was better with software-guided insulin dosing, as shown by a lower mean BG level ($P<.001$) and a greater percentage of time spent in the target range ($P=.0001$) (Figure 2). In addition, there was less hypoglycemia with software-guided insulin dosing ($P=.04$). There was also less GV with software-guided insulin dosing, as shown by decrements in standard deviation from the mean, CV, MAGE, and a decreased GPI. Decreased GV was present in patients admitted to the ICU with APACHE II scores either less than 20 or higher (Figure 3). Finally, an interaction term between protocol and diabetes status was added to multivariable regression models to examine whether the computer protocol improved the glucose control differently for patients with or without diabetes. The interaction was nonsignificant for the mean/SD, CV, GPI, and MAGE ($P>.10$).

DISCUSSION

The chief finding of this study is that software-driven guidance of intensive intravenous insulin successfully achieved glycemic control while lessening hypoglycemia and GV. This is one of the first studies to control all 3 domains of glycemic dysregulation, ie, hyperglycemia, hypoglycemia, and GV, each of which is known to be associated with increased mortality.

The link between GV and ICU mortality has only recently been shown. Mackenzie et al[10] studied 3434 ICU admissions to examine the effect of 13 different glycemic

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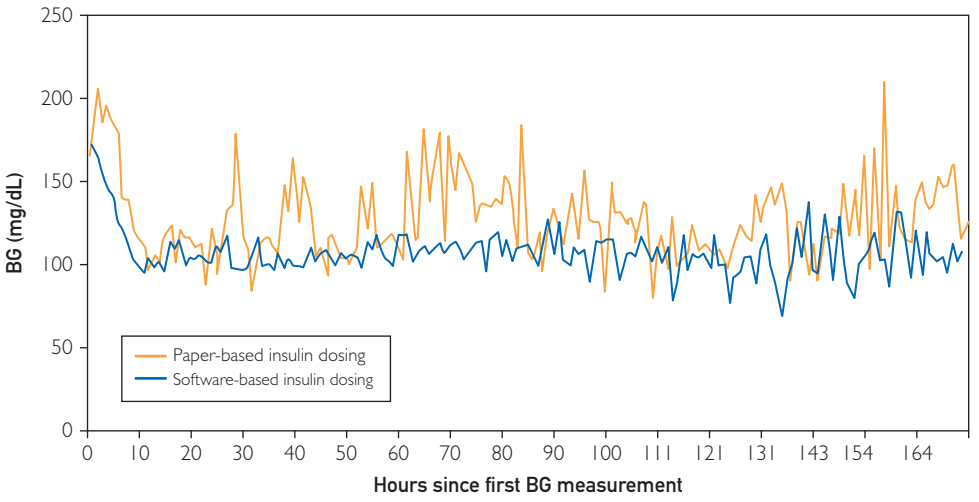
TABLE 2. Comparison of the Glycemic Results in the 2 Groups[a,b,c]

Variable	Paper-based group (n=110)	Software-guided group (n=87)	*P* value[d]	*P* value[e]
Admission BG (mg/dL)	156±60	181±45	.003	.04
Mean[f] BG (mg/dL)	135±34	117±16	<.001	.02
Median[g] BG (mg/dL)	130±30	109±15	<.001	.05
Q1	114	98		
Q3	138	127		
Range	73-287	79-388		
Time to reach target (h)	12.9±47	3.8±2.8	.09	.21
Time in target range (95-135 mg/dL) (%)	52±25	68±18	<.001	.01
Time >180 mg/dL (%)	12.5±20.9	8.3±18.9	.14	.38
Time >135 mg/dL (%)	37.8±29.1	26.7±27.2	.006	.007
Time <70 mg/dL (%)	1.44±3.6	0.51±1.1	.04	.25
Time <40 mg/dL (%)	0.30±1.3	0.14±0.9	.56	.68
BG tests per patient per day (No.)	8±4	17±6	<.001	<.001
Time between BG tests (h)	7.00±10.0	3.7±18.0	.33	.16
Patients with any BG >180 mg/dL (%)	55.4	42.5	.07	.87
Patients with any BG >135 mg/dL (%)	79.1	78.2	.87	.72
Patients with any BG <70 mg/dL (%)	31.8	31.0	.91	.12
Standard deviation of BG	42±40	29±15	.01	.02
Coefficient of variation	27.1±16.8	24.8±10.2	.47	.20
GPI	39±17	26±12	<.001	.01
MAGE	93±111	59±41	.009	.03
Final BG at ICU discharge (mg/dL)	145±60	99±27	<.001	.001

[a]BG = blood glucose; GPI = glycemic penalty index; ICU = intensive care unit; MAGE = mean amplitude of glycemic excursions.
[b]SI conversion factor: To convert BG values to mmol/L, multiply by 0.0555.
[c]Values recorded as mean ± SD from the mean except when indicated otherwise.
[d]*P* values from simple 2-sample *t* tests for continuous outcomes or χ^2 tests for binary outcomes without adjusting for other factors.
[e]*P* values from multivariable linear regression for continuous outcomes or multivariable logistic regression for binary outcomes adjusting for age, sex, diabetes status, and Acute Physiology and Chronic Health Evaluation II score.
[f]Mean of each individual patient's BG level.
[g]Mean and standard deviation of per-patient median BG, therefore presented as mean ± SD.

metrics of central tendency, variability, and minimum value on patient outcome. They not only verified that glycemic dysregulation predicts mortality but also found that hyperglycemia, hypoglycemia, and GV are synergistic and, in combination, strengthened the likelihood of death.[10] Krinsley[9,11] found that the link between mortality and GV was strongest in patients with average blood sugar measurements in the euglycemic spectrum. It has also recently been observed that insulin sensitivity is decreased in the first 24 hours of an ICU stay, which makes variability and hyperglycemia more likely to occur.[33] In addition, multiple experimental models suggest that intermittent hyperglycemia stimulates apoptosis more so than persistent hyperglycemia.[12,43,44] In humans, oxidative stress to endothelial cells is magnified with fluctuating glucose levels compared with steady-state hyperglycemia, a phenomenon that is independent of the severity of hyperglycemia.[45] These findings reinforce the importance of insulin delivery systems that control the individual elements of glycemic derangement.

There are 3 general categories of insulin management systems in ICU use. The most simple system consists of the insulin sliding-scale–inspired algorithm, which usually manifests as a paper-based protocol, although it is sometimes rendered by bedside computer. These paper-based protocols commonly require manual calculation and documentation based on a single BG measure, without consideration of the recent historical BG levels or patient insulin sensitivity and response to previous dosing.[46] The usual algorithm is one of "if-then" in action, although it may be complex, as was the one used in the NICE-SUGAR (Normoglycemia in Intensive Care Evaluation–Survival Using



Protocol	N0	N10	N20	N30	N40	N50	N60	N70	N80	N90	N100	N111	N121	N131	N143	N154	N164
Paper	110	82	77	70	64	61	57	51	47	41	38	37	36	35	32	32	32
Software	87	70	60	53	45	39	35	31	27	23	21	20	20	18	18	18	18

FIGURE 2. Blood glucose (BG) levels vs time mapped hourly for 7 days. The mean ± SD BG value for each patient was calculated and totaled for the baseline and intervention groups for each hour during the first 7 days of intensive care unit stay. Patients not tested during the hourly intervals are not included in the group value for that interval. The number of patients included in the group at each interval (N) are shown in the table accompanying the figure. Software-guided insulin dosing was superior to paper-based insulin dosing in smoothing out glycemic fluctuations throughout the 1-week sample period. To convert BG values to mmol/L, multiply by 0.0555.

Glucose Algorithm Regulation) study that was 6 pages long and required 56 "action codes" by the nurse.[17] Nursing compliance with paper-based protocols is sometimes capricious and frequently poor in the very demanding clinical setting.[20-22] Typical of insulin sliding scales, aggressive use of this kind of protocol to achieve tight glycemic control occurs at the expense of inducing iatrogenic hypoglycemia and GV.[30,47] A variant of this is the insulin dosing scheme used in the Van den Berghe studies, which is paper guideline based but also incorporates intuitive decision making by an experienced bedside nurse, who has the latitude to administer the amount of insulin deemed appropriate in the setting of changing conditions (eg, discontinuation of enteral feeding and recently administered corticosteroids).[3,36] The third category of insulin management is that of a computerized application that enables rapid, mathematical error—free, complex calculations that incorporate insulin sensitivity factors and previous BG values for recommended insulin infusion rates.[38,39,48-50]

Software-guided insulin dosing is receiving increased attention[37-39] and clearly achieves normoglycemic targets.[45-47,51,52] The advantages are (1) it forces more BG monitoring, as shown herein; (2) it allows patient-specific insulin dosing based on insulin sensitivity; (3) it safely adjusts to rapidly falling BG levels; and (4) it creates an instant database for observation of trends. Early evidence indicates that the frequency of glucose monitoring increases glycemic control[53] and decreases hypoglycemia.[52] This may be a significant factor in our improved glycemic control in the software-guided group as the frequency of measurements and intervals between measures were significantly different in the 2 groups despite the fact that the software was programmed for a measurement schedule identical to that of the paper-based protocol. To our knowledge, there are no studies comparing insulin

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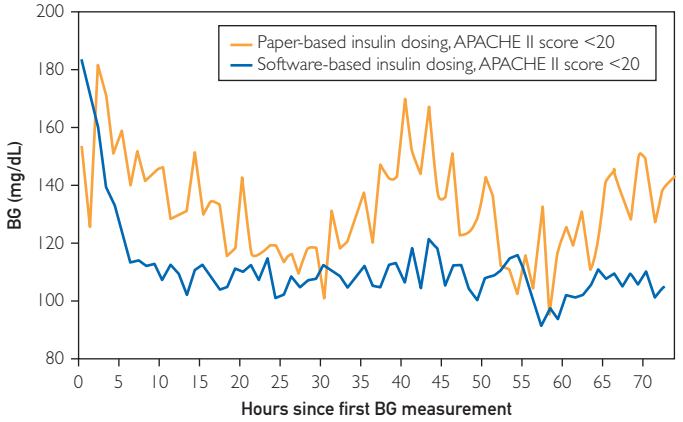
dosing software programs head-to-head. This pilot study used the GlucoStabilizer, which has previously been shown to be efficacious in achieving tight glycemic control[37] while also lessening hypoglycemia.[39] It has been postulated that targeting decreased variability will provide a survival advantage once attributed to euglycemia without the associated hypoglycemia and its deleterious adverse effects.[27] This study demonstrates that an insulin dosing strategy aimed at decreasing hyperglycemia can also decrease GV and hypoglycemia at the same time.

This study has inherent limitations. It is a retrospective pilot trial at a single institution, and although the sample size was small, the impact of the software-guided insulin dosing was clearly appreciated. A larger study to examine the difference in outcomes is planned. Also, it could be argued that the differences in glucose control may partly be due to the greater number of measurements obtained in patients whose insulin dosing was software guided. This is an important advantage of software tools that support better patient care as evidenced in this work, and the additional contributions of the software, including alarms to alert the nurse to measure the BG level, the complex algorithm used to calculate the insulin dose on the basis of patient-specific response, and the error-free calculation likely all contributed to better glycemic control. Protocol compliance, also believed to be an important consideration in achieving glycemic control, was not examined in this comparison because it was not measured for use of the paper-based protocol and would be difficult to measure retrospectively.

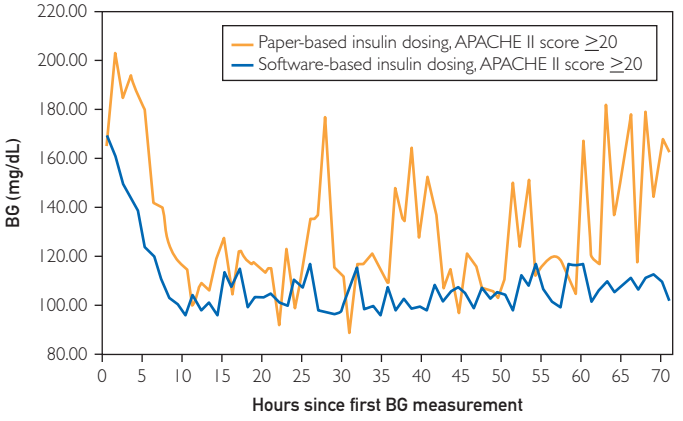
In addition, because bedside glucometer values have been shown to be less accurate than laboratory-measured values, especially in critically ill patients, it would have been optimal to obtain all the BG measurements in a manner that ensures laboratory accuracy.[18,54-57] However, most hospitals that depend on the ubiquitous availability of bedside glucometers do not presently find it practical, timely, or affordable to use devices of laboratory standard accuracy when managing critically ill patients with intensive insulin therapy.

Finally, the GV measures examined for this study are the most commonly reported measures that are clinically relevant, but they have various strengths and weaknesses in



A

Protocol	N0	N10	N20	N30	N40	N50	N60	N70
Paper	85	60	55	48	44	42	39	34
Software	77	60	51	44	36	32	28	25



B

Protocol	N0	N10	N20	N30	N40	N50	N60	N70
Paper	25	22	22	22	20	19	18	17
Software	10	10	9	9	9	7	7	6

FIGURE 3. Blood glucose (BG) levels vs time stratified by severity of illness (Acute Physiology and Chronic Health Evaluation II [APACHE II] scores [A] <20 and [B] ≥20) hourly during the first 72 hours. The mean ± SD BG value for each patient was calculated and totaled for the baseline and intervention groups for each hour during the first 3 days of intensive care unit stay. Patients not tested during the hourly intervals were not included in the group value for that interval. The number of patients included in the group at each interval (N) are shown in the table accompanying the figure. Software-guided insulin dosing was superior to paper-based insulin dosing in smoothing out glycemic fluctuations independent of severity of illness, as depicted by APACHE II scores (A) <20 or (B) ≥20. To convert BG values to mmol/L, multiply by 0.0555.

application to this analysis. The GV measure most influenced by frequency of sampling (GPI) was clearly highly statistically significantly different in the 2 groups. However, important standard measures, including standard deviation and MAGE, were statistically significantly different as well. The CV measure showed no statistically significant difference, being a ratio of the mean over the standard deviation, which has an inflated variance in this analysis, and, therefore, significance is more difficult to detect.

CONCLUSION

Converting from a paper-based protocol to a software-guided dosing method for intensive insulin therapy resulted in superior control of hyperglycemia and marked decrements in the incidence of hypoglycemia and GV. To our knowledge, this is the first time that an intensive insulin strategy has been shown to control all 3 glycemic derangements in critically ill patients. Going forward, the next investigative step should be to take a larger sample size of sicker patients and test the hypothesis that the application of software-guided insulin dosing will result in improved clinical outcomes from controlled glycemic derangements.

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Abbreviations and Acronyms: **APACHE II** = Acute Physiology and Chronic Health Evaluation II; **BG** = blood glucose; **CV** = coefficient of variation; **GPI** = glycemic penalty index; **GV** = glycemic variability; **ICU** = intensive care unit; **MAGE** = mean amplitude of glycemic excursions

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