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ORIGINAL ARTICLE

Computerization of the Yale Insulin Infusion Protocol and Potential Insights into Causes of Hypoglycemia with Intravenous Insulin

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Abstract

Background: The management of critically ill hyperglycemic patients in the intensive care unit (ICU) has been fraught with recent controversy. Only one randomized trial has demonstrated a mortality benefit to intensive glycemic control, with all subsequent studies failing to confirm this benefit and revealing a markedly increased risk of severe hypoglycemia (SH) in intensively treated patients. In most of these trials, adherence to the protocols were neither tracked nor reported.
Methods: A retrospective analysis of all patients admitted to an ICU who were treated with an insulin infusion directed by the GlucoCare™ IGC System, an FDA-cleared insulin-dosing calculator (Yale 100–140 mg/dL protocol). Mean blood glucose (BG) levels, time to target range and incidence of SH (< 40 mg/dL) and moderate hypoglycemia (MH) (40–69 mg/dL) were determined, and potential causes of hypoglycemic episodes were assessed.
Results: Mean post-target BG was approximately 123 mg/dL. Of > 55,000 readings in 1,657 patients, overall incidence of SH was 0.01% of readings and 0.3% of patients. MH occurred in 1.1% of readings and 17.6% of patients. The top potential causes of MH were: (1) Protocol-directed recommendations including continuation of insulin with BG < 100 mg/dL and decreases in the frequency of BG checks (63.7%), and (2) Staff non-adherence to protocol directives (15.3%).
Conclusions: The results of the GlucoCare-directed Yale 100–140 mg/dL protocol experience revealed an extremely low incidence of SH and an incidence of MH of 1.1%. The incidence of SH in this study was lower than the *control group* of the NICE-SUGAR study and are supportive of the new Society of Critical Care guidelines to target BG levels of 100–150 mg/dL in critically ill patients. Further refinements to the original protocol and emphasis on staff adherence to protocol directives could potentially further reduce these very low hypoglycemia rates.

Introduction

The management of critically ill hyperglycemic patients in the intensive care unit (ICU) has been fraught with controversy. In 2001, a single-center randomized study was the first to suggest that achieving a normal range of blood sugar levels in critically ill patients reduced mortality.[1] Since then, however, multicenter randomized trials have been unable to replicate these findings.[2–9] Their failure has been ascribed by some to be secondary to the significantly higher incidence of severe hypoglycemia (SH) (< 40 mg/dL) that accompanies intensive glucose management with intravenous insulin. It is important to note that the efficacy and safety of the protocols utilized in the trials were not previously reported or critically evaluated. Nonetheless, based on these data, the American Association of Clinical Endocrinologists and the American Diabetes Association have recommended that blood sugar levels in critically ill patients be maintained in a moderate to mildly hyperglycemic range of 140–180 mg/dL.[10,11] However, recently, the Society of Critical Care Medicine published their new guidelines that recommend a target range of 100–150 mg/dL based on their review of the literature.[12]

Along with the lack of proven safety/efficacy of the protocols utilized in the trials, actual adherence to the glucose control protocols was neither tracked nor reported. In the original study, an experienced team of researchers were in direct control of all of the insulin infusion adjustments,[1] whereas in the subsequent multicenter trials, protocol management was left to the patient's caregivers. Insulin dose calculations are indeed complex, time-consuming, and prone to error.[13–19] Several investigations have demonstrated that automation of "paper" protocols via insulin-dosing calculators can enhance compliance, reduce errors, and improve glucose control.[18–23] In the original Yale protocol articles, adherence to the published algorithm was not assessed.

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Accordingly, its reported metrics of glycemic control could never be assessed in the context of how precisely the protocol was actually followed. This study has two distinct objectives: (1) to describe the results of the use of the GlucoCare™ IGC System (Pronia Medical Systems, LLC, Louisville, KY), a Food and Drug Administration (FDA)–cleared insulin-dosing calculator based on the 2004 Yale insulin infusion protocol (target, 100–140 mg/dL), in more than 1,650 patients and (2) to report a critical analysis of all hypoglycemic events occurring during use of the protocol, so as to determine its baseline efficacy.

Subjects and Methods

The GlucoCare IGC System was 510(k) cleared by the FDA in August, 2008 with a target of 100–140 mg/dL based on the published and widely used Yale insulin infusion protocols.[24] (A separate lower target of 90–120 mg/dL was also available based on a second publication from the Yale group,[25] but it is rarely used by hospitals; this report includes only those implementing the original protocol.) The key feature of the Yale protocols that distinguish them from previously published guidelines is the customization of the infused insulin rate to a patient's individual response to prior rates; through this dynamic process, the Yale protocol essentially adapts to the patient's degree of insulin sensitivity. This is accomplished by determining the change in blood glucose (BG) concentrations over time for any given insulin infusion rate and incorporating these data into the next hour's recommended rate. Of note is that, because of this technique, the protocol eventually adapts to the administration of intravenous dextrose or any continuous parenteral or enteral nutrition. Similarly, the patient's diabetes status (i.e., type 1 vs. type 2) does not need to be considered until the transition to subcutaneous insulin injections. The protocol, however, is not intended for patients who are consuming intermittent meals, which must be handled separately from the protocol's specific directions.

Clinical use of GlucoCare began in January 2009, and the data for this study were gleaned from multiple institutions and analyzed in aggregate. Early results of the clinical use of the software demonstrated no episodes of SH (BG < 40 mg/dL) and a 1% incidence of moderate hypoglycemia (MH) (BG 40–69 mg/dL). Because of these results, and with the approval of our institutional users, the target range of 100–140 mg/dL was not changed to the guidelines of 140–180 mg/dL suggested by the American Association of Clinical Endocrinologists/American Diabetes Association.[10,11] As this is a retrospective study from multiple hospitals, no standardization of glucose meters or method of obtaining glucose readings occurred. Nurses, however, were extensively and uniformly trained on the use of GlucoCare prior to implementation at their hospital ICU.

In brief, GlucoCare is installed on the hospital system, and after a point-of-care BG result is obtained (typically a bedside capillary BG meter), the result is hand-entered by the nurse into GlucoCare. After the system calculates the insulin infusion rate change, based on the Yale protocol, this recommendation is then displayed for the nurse, who then confirms

BG 75-99 mg/dL	BG 100-139 mg/dL	BG 140-199 mg/dL	BG >200 mg/dL	INSTRUCTIONS
		BG ↑ > 50 mg/dL/hr	BG↑	↑INFUSION by "2Δ"
	BG ↑ by > 25 mg/dL/hr	BG ↑ 1-50 mg/dL/hr **OR** **BG UNCHANGED**	**BG UNCHANGED** **OR** BG ↓ 1-25 mg/dL/hr	↑ INFUSION by "Δ"
BG ↑	BG ↑ by 1-25 mg/dL/hr **BG UNCHANGED, OR** BG↓1-25 mg/dL/hr	BG ↓ by 1-50 mg/dL/hr	BG ↓ by 26-75 mg/dL/hr	**NO INFUSION CHANGE**
BG UNCHANGED **OR** BG ↓ by 1-25 mg/dL/hr	BG ↓ 26-50 mg/dL/hr	BG ↓ by 51-75 mg/dL/hr	BG ↓ by 76-100 mg/dL/hr	↓ INFUSION by "Δ"
BG ↓ by > 25 mg/dL/hr *See below*‡	BG ↓ by > 50 mg/dL/hr	BG ↓ by > 75 mg/dL/hr	BG ↓ by > 100 mg/dL/hr	HOLD x 30 min, then ↓ INFUSION by "2Δ"

‡ D/C INSULIN INFUSION: Check BG q 30 min; when BG ≥ 100 mg/dL, restart infusion @ 75% of most recent rate.

CHANGES IN INFUSION RATE ("Δ") are determined by the current rate:

Current Rate (Units/hr)	Δ = Rate Change (Units/hr)	2Δ = 2X Rate Change (Units/hr)
< 3.0	0.5	1
3.0 – 6.0	1	2
6.5 – 9.5	1.5	3
10 – 14.5	2	4
15 – 19.5	3	6
20 – 24.5	4	8
≥ 25	≥ 5	10 (ConsultMD)

FIG. 1. Main instructions from the 2004 Yale Insulin Infusion Protocol (100–140 mg/dL). See column 1, row 4 of the first table which demonstrates the recommendation that insulin continue with a BG decrease of 1–25 mg/dL even while in the range of 75–99 mg/dL.

that the change was made. An audible alert occurs when the next glucose reading is due, typically in 1 h. GlucoCare tracks all glucose levels and insulin-dosing recommendations and changes. Other demographic data (e.g., admitting diagnosis, age, diabetes type) were not recorded in GlucoCare and are not available for this analysis. Frequency of glucose checks varies from 15 min when patients are at risk for hypoglycemia (rapidly falling BG levels or BG levels below the target range) to up to every 4 h in those patients who have demonstrated glycemic stability. Users have the ability to decline or override all recommendations, allowing for clinical judgment to be considered (as in the case when tube feeds have recently been stopped). All such "protocol deviations" along with time delays are recorded and available in real time to clinical and administrative staff.

A detailed and critical analysis of all episodes of MH (BG 40–69 mg/dL) and SH (BG < 40 mg/dL) occurring in those patients who reached the target BG range of 100–140 mg/dL was performed, where the etiology of each episode of hypoglycemia was determined. GlucoCare reports the incidence of hypoglycemia in graphic format, providing access to BG readings at an individual patient level and in aggregate for all patients on the system, including the BG history for that patient, the insulin-dosing recommendations and actions, and any related text documentation.

Each hypoglycemic reading was individually analyzed and categorized as follows: (1) no clear etiology; (2) protocol deviation (e.g., failure to give dextrose when directed by GlucoCare or a late BG determination, defined as > 50% delay in protocol-directed interval [i.e., > 30 min delay in every 1-h check, > 1 h delay during every 2-h check]); (3) protocol-directed continuation of insulin with a BG < 100 mg/dL (Fig. 1) (if the current BG level decreased by 1–25 mg/dL from the previous glucose measurement, the protocol directs the insulin infusion to be decreased but not stopped, down to a glucose reading of 75 mg/dL); (4) protocol-directed every 2-h or every 4-h BG checks (this only occurs when the BG is within the target range for four sequential readings); or (5) protocol-directed automatic restarting of insulin after cessation of the drip for a rapidly falling or low glucose level. When events were analyzed, attention was paid to the immediately pre-hypoglycemic BG readings so as to glean further information regarding possible causes for the hypoglycemic event. Glucose levels clearly entered in error were excluded (e.g., BG of 1 mg/dL, associated with note that stated "real level was 129" mg/dL).

Results

Initial experience with a computerized version of the Yale protocol

In total, 1,657 patients have been treated with GlucoCare, incorporating 55,162 BG readings. Patients were treated in a variety of ICUs, including cardiothoracic ($n = 1{,}067$), coronary care ($n = 48$), medical ($n = 61$), burn ($n = 24$), mixed medical-surgical ($n = 184$), neurological ($n = 4$), non–cardiothoracic surgical ($n = 73$), and organ donors ($n = 196$). Mean blood sugar level after reaching the target was 123.6 mg/dL (range, 122.4 mg/dL in the cardiothoracic surgical unit to 151.4 mg/dL in the neurointensive care unit). Overall, 92.4% of patients reached the target range (100–140 mg/dL) after an average of 4.3 h (range, 3.9 h in the cardiothoracic surgical unit, 7.4 h in the surgical intensive care unit, and 9.2 h in the neurointensive care unit). Overall, 93.3% of glucose readings after reaching the target were maintained between 70 and 180 mg/dL.

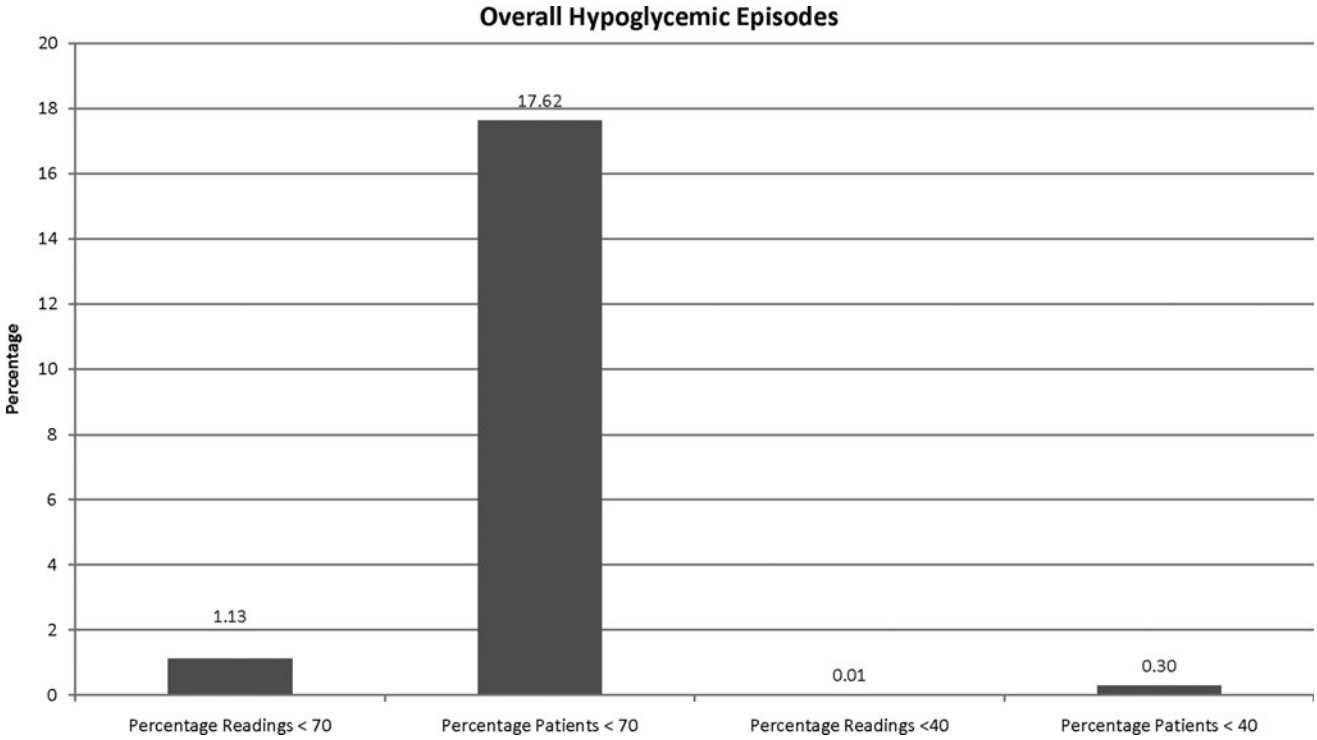

FIG. 2. Overall hypoglycemic episodes. Blood glucose cutoff values are in mg/dL.

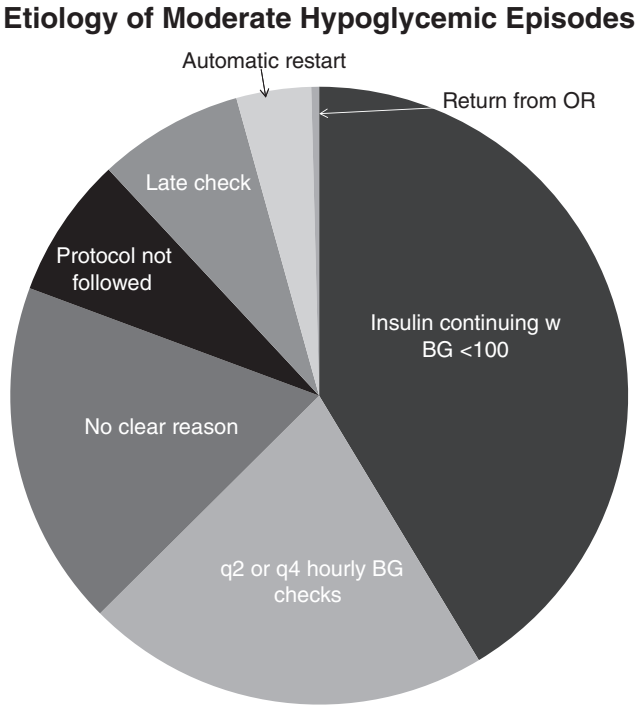

FIG. 3. Etiology of moderate hypoglycemic episodes. BG, blood glucose; OR, operation room; q2 or q4, every 2 h or 4 h.

The incidence of SH and MH by glucose reading and by patient is presented in Figure 2. Six readings were excluded based on clearly erroneous data entry. Of the total of >55,000 readings, a reading of <40 mg/dL occurred six times in a total of five patients (one reading of 24,144 cardiothoracic surgical unit readings [0.004%], four readings of 8,378 readings [0.05%] occurring in three burn unit patients, and one reading that was more than 3 h late [which occurred despite repeated GlucoCare-issued alarms]). Three of the four SH episodes in burn unit patients occurred after every 2-h checks (one reading followed an every 2-h check with the insulin infusion running at 13 U/h).

Exploratory assessment of hypoglycemic events

In total, 477 BG measurements 40–69 mg/dL occurred and were analyzed as to their cause. Etiologies of MH are depicted in Figure 3. Figure 4 depicts the incidence of hypoglycemia by ICU setting type. Of the 477 readings, 18.4% ($n=88$) of readings had no clear explanation, based on the aforementioned categorization. Protocol deviations were associated with 15.3% ($n=73$) of the MH readings. These included failure to give 50% dextrose (D50) as recommended by the protocol leading to continued low or decreasing BG level (7.5%, $n=36$) and/or late glucose checks (7.8%, $n=37$). It is important to note that 42.1% ($n=201$) of the hypoglycemic readings occurred in the setting of protocol-directed continuation of insulin while below the low target range of 100 mg/dL (Fig. 1). An additional 21.6%

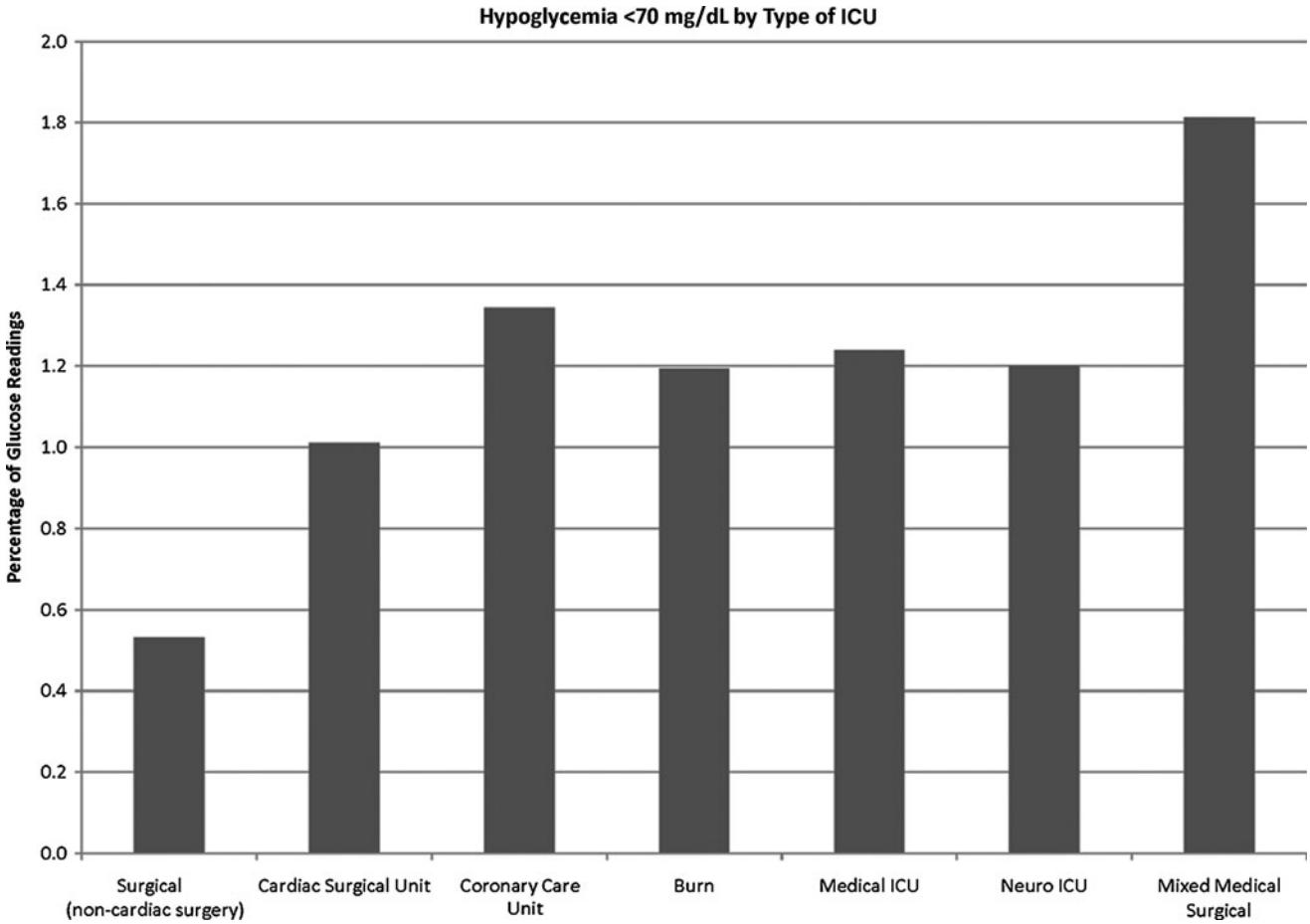

FIG. 4. Hypoglycemia <70 mg/dL by type of intensive care unit (ICU).

($n = 103$) occurred with the first reading after or within three protocol-directed every 2-h or every 4-h readings.

The Yale protocol directs users to automatically restart the insulin after cessation of the infusion for rapidly decreasing BG or low BG level; this occurs once the BG level rises above 100 mg/dL. This accounted for 4.0% ($n = 19$) of low readings in that after restarting the insulin infusion, the patient experienced an episode of MH. In total, protocol-directed insulin-dosing adjustments or frequency of BG measurements contributed to nearly 70% of all MH episodes; an additional 15.3% occurred in the setting of protocol deviations.

Discussion

The original Yale protocol utilized a target range of 100–140 mg/dL, and experience with its paper-based insulin-dosing recommendations in a medical ICU population was published in 2004.[24] Although this cannot be considered a direct comparative study, given different hospitals and patient populations, our results appear to compare favorably with that report,[24] where the mean time to achievement of the target range was 10 h (with ours being 8.6 h). Moreover, the SH prevalence in the 2004 publication was 0.05% of readings and 5.8% of patients; ours were 0% and 0%, respectively, in our medical ICU population. The rate of <60 mg/dL reported in the original manuscript[24] was 0.34% of readings and 23.1% of patients. With our computerized version, the respective results were 0.31% of readings and 9.5% of patients.

The results reported herein are consistent with other studies comparing computerized insulin-dosing calculators with paper-based protocols.[18–23,26] These have revealed less hypoglycemia and improved adherence to the protocol. Other studies have demonstrated that even experienced clinicians following complex paper protocols often make critical mistakes that lead to unwarranted hypo- or hyperglycemic excursions.[14–17] What computerized systems do is standardize the timing of insulin adjustments and reduce the errors in the calculations, two crucial factors related to preventing these glycemic fluctuations.

Our study also demonstrates that the Yale protocol, a widely used and popular algorithm for insulin infusion, has inherent directives, which could be easily modified, that might contribute to low BG readings. Specifically, the protocol recommends the continuation of insulin even when the BG level falls below the lower target range of 100 mg/dL. This only occurs in the setting that the BG level is falling by between 1 and 25 mg/dL from the prior reading. Although causality cannot be proven, this scenario was found to be associated with 42.1% of all MH episodes. An additional protocol-related issue is that 21.6% of MH events occurred when the protocol directed BG reading intervals longer than 1 h. The protocol recommends longer BG check intervals only when the BG readings are within the 100–140 mg/dL range for four consecutive intervals.

An additional 15.3% of MH events was associated with protocol deviations or late readings, which occurred despite alarms that notify personnel of needed BG readings. Accordingly, a total of up to 79% of hypoglycemic readings could potentially be prevented by additional modifications to this protocol and/or better compliance with current protocol directives.

It is interesting that experience with the use of the GlucoCare-directed Yale 100–140 mg/dL protocol has realized an incidence of SH (0.3% of patients) comparable to the historically extremely low rate in the control group of the NICE-SUGAR trial[21] (0.5% of patients with a target of 140–180 mg/dL). Our SH rate among ICU patients exclusive of cardiothoracic surgical units (NICE-SUGAR excluded these patients) and burn units (not a common patient population in most hospitals) was 0%. Our data suggest that perhaps the use of technology can allow for "more normal" BG targets with an acceptable risk of SH and MH.

Recently, the NICE-SUGAR investigators[27] published post hoc data from their trial that demonstrated a 40% increase in mortality in those patients who experienced even MH. Although a cause-and-effect relationship cannot be concluded, it would appear to be a reasonable goal to avoid even such mild to moderate hypoglycemic ranges in critically ill patients. In addition, the Society of Critical Care Medicine published their recommendations that the BG targets be modified to 100–150 mg/dL in critically ill patients based on the authors' review of the available literature.[12] The target range of this study is consistent with those recommendations, and our results demonstrate that this newly suggested range can be targeted with a low risk of hypoglycemia in the appropriate setting.

There are several weaknesses in this study. As this was not a comparative study, there is no paper or computer-based protocol to which these results can be directly compared. In addition, the study is limited in that admitting diagnosis, age, and other key demographic data were not gathered for a more detailed analysis of the patients. However, the large number of patients and the detailed analysis of the episodes of hypoglycemia are relative strengths.

Conclusions

The results of this study demonstrate that through the use of GlucoCare, an FDA–cleared, automated insulin-dosing calculator, lower targets than those currently recommended by AACE/ADA (140–180 mg/dL) can be achieved with an extremely low incidence of SH, which in this study with a target of 100–140 mg/dL was lower than the control group (140–180 mg/dL) in the NICE-SUGAR study.[3] These data call into question the need to raise the target range for glucose control in all critical care settings and are consistent with the newly recommended target range of 100–150 mg/dL by the Society of Critical Care Medicine.[12] Lower targets may therefore be warranted if they can be achieved safely. Of course, only well-designed and controlled randomized studies can provide a definitive answer to the question as to whether euglycemia in the critically ill—with the avoidance of hypoglycemic episodes—improves clinical outcomes.

Author Disclosure Statement

M.R.M. and B.J.B. are co-founders of Pronia Medical Systems, LLC, the developer of the GlucoCare IGC System. S.E.I. declares no competing financial interests exist.

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