Original Article

INSULIN INFUSION PROTOCOLS FOR CRITICALLY ILL PATIENTS: A HIGHLIGHT OF DIFFERENCES AND SIMILARITIES

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ABSTRACT

Objective: To discuss the major differences and similarities among the currently published insulin infusion protocols (IIPs) for critically ill patients.

Methods: IIPs were identified by searching MEDLINE, EMBASE, and the Cochrane Central Register of Controlled Trials. The reference lists for all retrieved protocols were also reviewed to identify any IIPs that were not surfaced with use of our initial search strategies. The major differences and similarities among the IIPs were identified and examined. In addition, strategies for successful implementation of IIPs were outlined.

Results: Our search strategies retrieved 17 IIPs. Currently, no published studies have compared one insulin protocol with another. The major differences or similarities among the published IIPs were in the following areas: patient characteristics, target glucose level, time to achieve target glucose level, incidence of hypoglycemia, rationale for adjusting the rates of insulin infusion, and methods of blood glucose measurements. Because of variations in the definition of hypoglycemia, methods of blood glucose measurement, and types of blood samples used, some comparisons across the protocols were difficult. Use of a multidisciplinary team and gaining administrative support are crucial for addressing issues and provision of necessary resources for implementing a protocol for "tight" glycemic control in critically ill patients.

Conclusion: Clinicians should evaluate the type of patients in their critical care units, the mean baseline glucose levels, and the available resources to determine the most appropriate and practical IIP for their institution. (**Endocr Pract. 2007;13:137-146**)

Abbreviations:
A1C = hemoglobin A1c; **ACE** = American College of Endocrinology; **CREATE-ECLA** = Clinical Trial of Reviparin and Metabolic Modulation in Acute Myocardial Infarction Treatment Evaluation-Estudios Cardiologicos Latin America; **DIGAMI** = Diabetes and Insulin-Glucose Infusion in Acute Myocardial Infarction; **GIK** = glucose-insulin-potassium; **ICU** = intensive care unit; **IIPs** = insulin infusion protocols

INTRODUCTION

Hyperglycemia is a common occurrence in critically ill patients with and without diabetes. Stress during critical illness increases the levels of counterregulatory hormones and cytokines associated with hyperglycemia (1). Medications, such as corticosteroids, epinephrine, and norepinephrine, which are commonly administered in the intensive care unit (ICU), may also result in elevated glucose levels (1). In addition, hyperglycemia may result from parenteral and enteral nutrition and from dextrose solutions that are commonly used for administration of drugs or fluids (1).

Hyperglycemia in critically ill patients has been associated with an increase in the rates of mortality, infections, acute renal failure, blood transfusions, and critical illness polyneuropathy (2-7). The poor outcomes noted in such patients may be the result of several proposed mechanisms, including impaired preconditioning, phagocyte destruction, platelet hyperactivity, inflammatory changes, cellular adhesion, and oxidative stress (8).

Glycemic control through the use of insulin infusion therapy has been shown to reduce morbidity and mortality significantly in acutely ill patients (2-7). Recently published studies have stimulated interest in managing hyperglycemia through the implementation of insulin infusion protocols (IIPs).

The purposes of this article are to summarize the benefits of "tight" glycemic control in critically ill patients

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and to highlight the differences and similarities among published IIPs. Furthermore, strategies that facilitate the implementation of IIPs in the critical care setting will be discussed.

EVIDENCE SUPPORTING IMPROVED OUTCOMES WITH TIGHT GLYCEMIC CONTROL

The clinical interest in tight glycemic control for critically ill patients increased after publication of the landmark studies by Malmberg et al (6,7,9) and Van den Berghe et al (2). Although the studies differed in the types of patients, the insulin infusion therapies, and the target glucose levels, they all concluded that hyperglycemia was an important predictor of mortality in critically ill patients.

In the first Diabetes and Insulin-Glucose Infusion in Acute Myocardial Infarction (DIGAMI 1) study, 620 patients with diabetes and acute myocardial infarction were randomized to receive either insulin-glucose infusions for at least 24 hours followed by multiple daily insulin injections or standard treatment (control group) (6,7). At baseline, the 2 groups did not differ in hemoglobin A1c (A1C). The reduction in A1C was greater in the insulin infusion group at 3 months (1.1% versus 0.4%; $P<0.0001$) and 1-year follow-up (0.9% versus 0.4%; $P<0.01$). The intensive insulin treatment group had a relative reduction in mortality of 30% ($P = 0.027$), and the effect was sustained for more than 3 years, with a relative reduction in mortality of 28% ($P = 0.011$).

The DIGAMI 2 study was designed to compare 3 treatment strategies in patients with type 2 diabetes who had had an acute myocardial infarction: group 1, acute insulin-glucose infusion followed by insulin-based long-term glucose control; group 2, insulin-glucose infusion followed by standard glucose control; and group 3, routine metabolic control according to local practice (9). The study, originally planned to recruit 3,000 patients, was stopped prematurely because of the slow patient recruitment. None of the patients randomized to the insulin-glucose infusion group achieved the primary fasting blood glucose target of 90 to 126 mg/dL. In addition, the mean fasting glucose levels (149 mg/dL) were similar among all groups. The results, based on 1,253 patients, showed no improvement in morbidity or mortality with insulin-glucose infusions, but an epidemiologic analysis of the data reported that the glucose level was a strong independent predictor of long-term mortality. The study demonstrated that insulin infusions in the absence of glucose-lowering results had no effects on outcomes.

Van den Berghe et al (2) studied the outcome in 1,548 patients admitted to the surgical ICU who were randomized to receive either conventional insulin treatment to maintain blood glucose levels between 180 and 200 mg/dL or intensive insulin therapy with target blood glucose levels between 80 and 110 mg/dL. At the conclusion of the study, the intensive care mortality rate was significantly lower in the intensive insulin therapy group (4.6%) than in the conventional treatment group (8.0%) ($P<0.04$). The results of intensive insulin therapy were even more pronounced among patients with an ICU length of stay greater than 5 days. Mortality rates were significantly lower among patients receiving intensive insulin therapy (10.6%) in comparison with patients receiving conventional treatment (20.2%) ($P = 0.005$). Tight blood glucose control also led to a 34% reduction in the overall in-hospital mortality rate, a 46% reduction of septicemia, a 41% reduction in acute renal failure necessitating dialysis, a 44% reduction in polyneuropathy, and a median reduction of 50% in the number of erythrocyte transfusions.

Furnary et al (3) investigated the effect of insulin infusion therapy versus intermittent subcutaneous insulin injections in 3,896 patients with diabetes undergoing cardiac surgical procedures. The study revealed a 57% reduction in the risk of death and a 66% reduction in the risk of deep sternal wound infections in patients receiving insulin infusion therapy ($P<0.0001$ for both). On further analysis, the mean blood glucose levels in patients without deep sternal wound infections were significantly lower in comparison with those who had deep sternal wound infections on postoperative days 1 and 2 ($P = 0.02$ and $P = 0.01$, respectively).

In a separate study, 1,600 patients admitted to the medical-surgical ICU underwent assessment for outcomes associated with improved glycemic control (4). The group receiving intensive insulin therapy had improved blood glucose levels in comparison with a retrospective control group: 130.7 mg/dL versus 152.3 mg/dL, respectively ($P<0.001$). Those patients with lower blood glucose levels had a 29.3% reduction in mortality and a 10.8% reduction in duration of stay in the ICU ($P = 0.02$ and $P = 0.01$, respectively).

The benefits of tight glycemic control in patients admitted exclusively to the medical ICU were studied by Van den Berghe et al (10) in a prospective, randomized, controlled trial. This study involved 1,200 patients who were admitted to the medical ICU and were expected to receive at least 3 days of intensive care. Similar to the trial conducted in the surgical ICU (2), patients were randomized to tight glycemic control to maintain blood glucose levels between 80 and 110 mg/dL or to conventional therapy to maintain blood glucose levels of 180 to 200 mg/dL. In the 767 patients who required prolonged ICU stay (≥3 days), a significant reduction in mortality was noted in the intensively treated group (relative risk reduction, 18.1%; absolute risk reduction, 9.5%; $P = 0.009$). In the intention-to-treat analysis for the entire cohort, morbidity in the intensively treated group was significantly reduced by decreasing ICU length of stay, preventing significant elevations in serum creatinine, and reducing ventilatory support time. The intensive insulin therapy, however, did not reduce in-hospital mortality in comparison with that in the conventional treatment group (37% versus 40%, respectively; $P = 0.33$). Among the 433 patients who stayed in the ICU less than 3 days, mortality was 18.8% versus 26.8% in the conventional and intensive treatment groups, respectively. After adjustments for baseline characteristics, including the acute physiologic assessment and chronic health evaluation (APACHE-2) score, the difference was not statistically significant ($P = 0.41$).

PROPOSED MECHANISMS FOR IMPROVED OUTCOMES WITH TIGHT GLYCEMIC CONTROL

Whether the protective effects of insulin or the tight glucose control achieved is responsible for the reported improved outcomes is unclear. One study reported improved outcomes associated with insulin infusion therapy independent of glucose control (11). Investigators randomized 940 patients with acute myocardial infarction to either continuous glucose-insulin-potassium (GIK) infusion or no infusion (11). In patients without signs of heart failure, the mortality at 30 days was significantly reduced in the GIK infusion group in comparison with the control group—1.2% versus 4.2%, respectively (relative risk, 0.28; 95% confidence interval, 0.1 to 0.75). This reduction in mortality was demonstrated with the GIK infusion group, despite the lack of difference between the 2 groups in blood glucose levels at the time of admission and in-hospital stay. These data may suggest that the protective effects of insulin are associated with improved outcomes, although the findings were not confirmed by 2 larger prospective studies, DIGAMI 2 (9) and the Clinical Trial of Reviparin and Metabolic Modulation in Acute Myocardial Infarction Treatment Evaluation-Estudios Cardiologicos Latin America (CREATE-ECLA) (12).

The DIGAMI 2 (9) and CREATE-ECLA (12) studies reported no improvement in mortality or morbidity with insulin infusions in patients with myocardial infarction. In the DIGAMI 2 study, no patients randomized to the insulin-glucose infusion group achieved the primary treatment target of fasting blood glucose of 90 to 126 mg/dL (9). Mean fasting glucose level (149 mg/dL) and A1C (6.8%) were similar among groups. Therefore, if euglycemia was predictive of outcomes, no differences would have been expected, and none was observed. In a large (N = 20,201) randomized international trial, CREATE-ECLA, the mean glucose level was 162 mg/dL in the GIK infusion group, and patients with higher baseline glucose levels had a higher mortality (12). These studies suggested that insulin infusions without achievement of normoglycemia did not improve clinical outcomes.

Finney et al (13) investigated outcomes associated with glycemic control in 523 patients admitted to the ICU. Excessive administration of insulin was associated with increased ICU mortality (odds ratio, 1.02 [confidence interval, 1.01 to 1.04] despite a glucose level of 111 to 144 mg/dL). This relationship was confirmed in another study that reported that large amounts of insulin appeared to be an independent risk factor for mortality in critically ill patients (14). In both studies, the patients had severe insulin resistance attributable to their underlying illness and therefore required high insulin doses (13,14). These data may suggest that lower levels of blood glucose and not insulin administration are associated with improved mortality, although this point remains controversial.

METHODS TO ACHIEVE GLYCEMIC CONTROL

Insulin, given either intravenously as a continuous infusion or subcutaneously, is considered the most effective agent to achieve glycemic control in the hospital setting (15). Historically, sliding scale insulin was considered the "gold standard" for the management of hyperglycemia in critically ill patients, although this approach produced suboptimal results. Insulin sliding scales tend to be reactive rather than proactive (16). The dose of insulin administered with sliding scale insulin is typically based on the inadequacy of the previous dose and does not correct the subsequent glucose levels (16). In addition, insulin sliding scales do not provide basal insulin coverage and generally involve the subcutaneous administration of insulin, which is associated with delayed onset of action, especially in critically ill patients who have poor peripheral circulation (17). The effectiveness of insulin sliding scales in the ICU may also be suboptimal, in light of the reported high rates of hyperglycemia, hypoglycemia, and iatrogenic diabetic ketoacidosis in hospitalized patients (15). Therefore, the American College of Endocrinology (ACE) (15) and the American Diabetes Association (8) discourage the use of insulin sliding scales as monotherapy to control hyperglycemia.

The ACE (15) and American Diabetes Association (8) recommend the use of intravenous insulin therapy in patients with critical illness. In comparison with subcutaneously administered sliding scale insulin, the intravenous route provides predictable insulin delivery and allows rapid control of glucose levels (18). Nevertheless, insulin infusions are considered more difficult and time consuming to prescribe and implement than are conventional therapies. Moreover, health care professionals generally fear a higher incidence of hypoglycemia with the use of insulin infusions. Standardized protocols may help facilitate the use of insulin infusion therapy and thereby achieve tight glucose control with a minimum of glucose fluctuations or adverse outcomes.

INSULIN INFUSION PROTOCOLS

Various IIPs have been published in the literature. We conducted a comprehensive literature search to identify all published IIPs for critically ill adult patients. The objective was to highlight the major differences and similarities among available protocols to help facilitate decision making regarding an appropriate IIP for a specific setting.

Methods and Criteria for Identifying Protocols

We identified IIPs by searching MEDLINE (January 1966 to March 2006), EMBASE (January 1980 to March 2006), and the Cochrane Central Register of Controlled Trials. In addition, the reference lists for all the protocols retrieved were reviewed to identify any additional IIPs that were not surfaced with use of our initial search strategies.

The following key words were used in the search strategies: algorithm, critical care, critical illness, critically ill, glucose control, insulin, insulin infusion, intensive care, intensive glucose, nomogram, and protocol.

The following were excluded from this review: meeting abstracts, articles in which a detailed description of the protocol was not provided, protocols that were not evaluated in a critical care setting, protocols evaluated only in a pediatric population, protocols evaluated primarily for the indication of myocardial infarction, protocols evaluated only in the perioperative setting, and those that were not published in the English language.

Major Differences and Similarities Among IIPs

Our search strategies retrieved 17 IIPs that met the inclusion criteria (Table 1) (2-4,17,19-31). All protocols were managed by the bedside nurse and required frequent glucose measurements, generally beginning with every 1 to 2 hours. The major differences or similarities among the protocols included the following: patient characteristics, target glucose level, time to achieve target glucose level, incidence of hypoglycemia, rationale for adjusting rates of insulin infusion, and methods of blood glucose measurement. We found no formal studies that directly compared the efficacy and safety of one protocol with another. The following material reviews the aforementioned major differences and similarities among the 17 retrieved published IIPs.

Patient Characteristics

Clinical characteristics have a role in influencing glycemic control and clinical outcomes. In one case-control study, poor glycemic control was predicted on the basis of the following factors: advanced age, history of diabetes, cardiac operation, postoperative complications, severity of illness, nosocomial infections, prolonged ventilation, and use of certain medications such as propofol, corticosteroids, and catecholamine infusions (14). Furthermore, acute insulin resistance in conjunction with poor glycemic control was associated with worse outcomes in patients without diabetes in comparison with patients who had diabetes (14).

The various hospital settings and patient populations in which the protocols were implemented are outlined in Table 1. Most of the protocols were evaluated in critically ill patients, except for 2 that were implemented in both ICU and non-ICU floors (3,29). Thus far, no reported studies have been conducted to determine whether a protocol evaluated in a specific ICU population can achieve similar responses and outcomes when implemented in a different ICU population.

All protocols included patients with hyperglycemia, with or without a prior history of diabetes. Kanji et al (28) raised a major issue about using the available IIPs in patients with type 1 diabetes mellitus. When a patient has a blood glucose level indicative of hypoglycemia, protocols require the nurse to discontinue the insulin infusion and administer dextrose. A patient with insulin-dependent diabetes, however, may be unable to utilize the extra glucose and may also be at risk for adverse events from intracellular hypoglycemia, despite subsequent normal glucose measurements (28). Therefore, according to the protocol reported by Kanji et al (28), insulin should not be discontinued completely in patients with “true” type 1 diabetes mellitus. All other protocols, including those evaluated exclusively in patients with diabetes, required the nurse to stop the insulin infusion and administer dextrose in all patients with a hypoglycemic blood glucose measurement. At present, studies have not been conducted to determine the clinical significance of this issue.

Protocol Target Glucose Level

Five of the identified protocols aimed at maintaining blood glucose levels <111 mg/dL (2,20,24,25,28), whereas the others chose to adopt a more conservative strategy. Targeting a glucose level <111 mg/dL may not be practical to implement in some ICU settings because of the severely elevated baseline glucose levels in critically ill patients or the lack of adequate resources. In the study by Van den Berghe et al (2), approximately 12% of the patients had baseline blood glucose levels >200 mg/dL. In other institutions, the incidence of hyperglycemia may be higher.

Implementation of strategies for tight glycemic control usually raises concerns about inadvertently elevating the incidence of hypoglycemia. In fact, Van den Berghe et al (2) reported a 5.1% incidence of hypoglycemia in patients randomized to the intensive treatment strategy, in comparison with 0.77% in patients randomized to conventional treatment. Although none of those cases of hypoglycemia was associated with hemodynamic deterioration or convulsions, some institutions may decide that available resources are inadequate to accommodate management of substantially higher incidences of hypoglycemia. Finally, some investigators have suggested that blood glucose levels <111 mg/dL may not be required in all critically ill patients, an opinion that may support the use of conservative glucose control in certain groups of critically ill patients (3,14,32).

The ACE supports a near-normal glucose level in all ICU patients and recommends 110 mg/dL as the upper limit for glycemic targets in the ICU setting (15). On the basis of the study by Van den Berghe et al (2), however, Bode et al (32) recommended a glucose target range of 80 to 110 mg/dL for insulin infusion therapy in critically ill

Table 1
Summary of Reported Insulin Infusion Protocols*

Reference	No. of pts†	Hospital setting	% DM	TGL (mg/dL)	BG measurement method	Hours to reach TGL	Definition and occurrence of hypoglycemia
Van den Berghe et al (2)	765	University medical ctr SICU	13	80-110	Glucose analyzer Arterial samples	NR	BG ≤40 mg/dL; IIP 5.1% vs conventional 0.77%
Zimmerman et al (19)	168	University medical ctr SICU (cardiac)	32	80-150	Accu-Chek Inform Venous samples	Median 2.1	BG <65 mg/dL; IIP 16.7% vs control 9.8% (*P* = 0.098) BG <40 mg/dL; IIP 7.1% vs control 2.9% (*P* = 0.084) BG <40 mg/dL; IIP ≤3% after IIP modified
Taylor et al (20) (Protocol 1)	95	University medical ctr SICU	51	120-150	Arterial line or finger stick	7.4	BG <40 mg/dL; IIP 1.1%-3.4% incidences
Taylor et al (20) (Protocol 2)	119	University medical ctr SICU	53	80-110	Arterial line or finger stick	13.6	BG <40 mg/dL; IIP 1.1%-3.4% incidences
Dilkhush et al (21)	30	Level II trauma ctr SICU	33	80-130	Capillary blood samples	Mean 12.6 (2-36)	BG <60 mg/dL; IIP 23.3%
Markovitz et al (22)	29	Community hosp SICU (cardiac)	100	120-199	Venous and capillary samples	NR	BG <70 mg/dL; IIP 1.4% of days vs control 5.1% of days
Goldberg et al (23) (Yale Protocol)	52	University medical ctr MICU	56	100-139	One Touch Sure Step Flex	Median 9	BG <60 mg/dL; 23% BG <40 mg/dL; 3 incidences
Bland et al (24)	5	University medical ctr MICU	NR	80-110	Accu-Chek Advantage Finger stick or arterial	NR	BG <40-60 mg/dL; IIP 80% vs control 60% BG <40 mg/dL; IIP 20% vs control 20% (*P* = 0.15)
Collier et al (25)	435	University medical ctr trauma ICU	9.2	80-110	NR	No patient achieved TGL	BG <60 mg/dL; 5% on any given day between IIP and control
Krinsley (4)	800	Community hosp MSICU	18.1	<140	Vitros Lab Analyzer Plasma or finger stick	NR	BG 40-59 mg/dL; IIP 1.02% vs control 0.54% (*P* = 0.89) BG <40 mg/dL; IIP 0.34% vs control 0.35% (*P* = 0.02)
Brown & Dodek (26)	77	University medical ctr MSICU	NR	126-207	Accu-Chek Capillary or chemistry—Vitros Lab	Median 2 (1-22)	Hypoglycemia requiring glucose; IIP 9.1% vs control 3.3%
Laver et al (27) (Bath Protocol)	27	District general hosp MSICU	NR	72-126	Accu-Chek Advantage Mostly arterial samples	NR	No. of readings from 40-54 mg/dL; IIP 6 vs control 3 No. of readings <40 mg/dL; IIP 3 vs control 0
Kanji et al (28)	50	University medical ctr MSICU	68	81-110	Accu-Chek Inform Capillary samples	11.3 ± 7.9	BG <40 mg/dL; IIP 4% vs control 16% (*P* = 0.046)
Chant et al (17)	44	University-affiliated hosp MSICU	32	90-144	Glucometer Elite Capillary samples	Median 15	BG <72 mg/dL; IIP 3.8% vs control 2.2% incidences (*P*<0.001) BG <40 mg/dL; IIP 0.2% vs control 0.4% incidences (NS)
Ku et al (29)	50	University medical ctr MSICU & non-ICU floors	56	80-180	Glucose meter (not specified)	Mean 3.5 ± 0.3	BG ≤60 mg/dL; IIP 14% vs control 25% BG ≤40 mg/dL; IIP 4% vs control 10.9%
Lien et al (30) (Duke Protocol)	28	University medical ctr MSICU	79	<150	NR	NR	BG <70 mg/dL; IIP 0.2 ± 0.5 occurrence/day; patient vs control 0.1 ± 0.3 (NS)
Furnary et al (3) (Portland Protocol)	? (total 4,864)	University medical ctr OR, SICU (cardiac), & non-ICU floor	100	100-150	Finger stick or arterial blood sample	3 (94% of patients)	BG <60 mg/dL; IIP 0.5% Symptomatic hypoglycemia; IIP 0.04%
Orford et al (31)	148	Level III ICU, MSICU	NR	74-126	Blood gas analyzer Whole blood sample	NR	BG <40 mg/dL; 4 occurrences BG 40-54 mg/dL; 43 occurrences

*BG = blood glucose; ctr = center; DM = diabetes mellitus; hosp = hospital; ICU = intensive care unit; IIP = insulin infusion protocol; MICU = medical intensive care unit; MSICU = medical-surgical intensive critical care unit; NR = not reported; NS = statistically nonsignificant; OR = operating room; SICU = surgical intensive care unit; TGL = target glucose level; vs = versus.
†Refers only to the number of patients who received insulin infusion therapy.

surgical patients and recommended moderate glucose target levels between 90 and 140 mg/dL for all nonsurgical ICU patients.

Despite the various previous recommendations for the target glucose levels in critically ill patients, the optimal value remains unclear. In one study (33), the lowest mortality rate was reported in patients with the tightest glycemic control. In this retrospective review of 1,826 patients, glucose levels during ICU stay were associated with hospital mortality, among a heterogeneous group of critically ill patients. The lowest mortality was reported in patients with mean glucose levels of 80 to 99 mg/dL, and the nonsurvivors had higher mean glucose levels than did the survivors. Another study (3), however, suggested that very tight glycemic control might not be required in all ICU patients. In patients with diabetes undergoing a cardiac surgical procedure, a blood glucose inflection point at 175 mg/dL was identified, at which the incidence of deep sternal wound infections began to increase significantly.

Rady et al (14) discouraged the use of a single target glucose value in all critically ill patients, without considering the characteristics of the patients and any concurrent medications or interventions. In that case-control descriptive study, mortality increased for patients without diabetes at a glucose level of 144 mg/dL and increased for patients with diabetes at a glucose level of 200 mg/dL (14).

Further research is needed to determine whether a single protocol would be sufficient for all critically ill patients or whether multiple ICU protocols with different target glucose levels are warranted. Recently, the Glucontrol Study was conducted to compare the effects of two glucose control regimens (target glucose 80 to 110 mg/dL versus 140 to 180 mg/dL) in a mixed ICU population. However, this prospective, randomized, multicenter study was stopped early because of safety concerns. In the tight control group, about 20% of those who developed hypoglycemia (defined as blood glucos <40 mg/dL) died, compared with 12% of patients who developed hypoglycemia in the conventional control arm ($P = 0.0002$) (34). The NICE-SUGAR study is a prospective, randomized, controlled study designed to compare two glucose control regimens (target glucose 81 to 108 mg/dL versus <180 mg/dL) in a heterogeneous population of ICU patients (35). The study is ongoing, with a target enrollment of 5,000 patients.

Time to Achieve Target Glucose Level

Because tight glycemic control is associated with reductions in mortality and morbidity, a logical goal would be to implement an insulin protocol that could eliminate hyperglycemia as rapidly and safely as possible. The published IIPs, however, were not comparable in terms of the time to achieve a target glucose level (Table 1).

The effectiveness of the IIPs was assessed in some studies by determining the ability of the protocol to achieve the desired target glucose level, although the methods used for assessment were not consistent. Some investigators reported the percentage of glucose values within the target range, others reported the percentage of time the patients' glucose levels were in control, and still others used the patients' mean blood glucose level to assess the protocols. In one study, the composite average of the daily mean blood glucose levels from the day of the surgical intervention and the first and second postoperative days was used as the indicator of protocol effectiveness (3).

Incidence of Hypoglycemia

All the reviewed insulin protocols reported the incidence of hypoglycemia; however, because the definition of hypoglycemia varied, comparison of the incidence of hypoglycemia across the protocols was difficult (Table 1). The definition of hypoglycemia in some studies (blood glucose <40 mg/dL) was lower than the threshold commonly used by physicians (<60 to 80 mg/dL) (2,20,28). Accordingly, the actual incidence of hypoglycemia, as defined by most clinicians, may be higher than the reported incidence in studies that used a lower glucose threshold to define hypoglycemia. Nevertheless, none of the protocols reported serious outcomes (that is, hemodynamic deterioration or seizures) in patients in whom hypoglycemia developed. In addition, with frequent monitoring of blood glucose levels, hypoglycemic events are expected to be mild, transient, and easily treated (36).

The definition of "clinically significant hypoglycemia" has not been clearly determined. Although the symptoms of hypoglycemia, such as sweating and decreased level of consciousness, may occur at plasma glucose values less than 40 mg/dL, the symptoms of neuroglycopenia may not be predicted on the basis of plasma glucose levels alone (31,37). In a study that evaluated 17 subjects without diabetes before and after insulin-induced hypoglycemia, the manifestations of neuroglycopenia did not correlate significantly with the nadir plasma glucose level or the duration of hypoglycemia (37).

In one study, the protocol was modified to include different insulin titration requirements for patients receiving corticosteroids and for patients with a history of diabetes (19). The modifications helped reduce the rate of occurrence of hypoglycemia from 7.1% to ≤3%. Patients with a history of diabetes and those receiving corticosteroid therapy utilized higher doses of insulin in comparison with other patients. Therefore, the protocol accounted for adjustments of insulin infusion in patients without diabetes or corticosteroid therapy while maintaining the same insulin infusion rate for patients with diabetes or receiving corticosteroid therapy.

In another study, the interruption of enteral or parenteral nutrition or dextrose solutions, while the insulin infusions were continued, was identified as a predisposing factor for hypoglycemic events that occurred during a 6-month pilot period (31). Therefore, the protocol designed required a constant caloric source and frequent monitoring of blood glucose levels to detect and prevent hypoglycemic episodes (31).

Although all studies concluded that hypoglycemia was infrequent, benign, and easily treated, the recent termination of the Glucontrol and VISEP studies has prompted some controversy (34,38). The VISEP (Efficacy of Volume Substitution and Insulin Therapy in Severe Sepsis) Trial was conducted by the German Sepsis Society to determine the influence of colloid versus crystalloid volume resuscitation and of intensive versus conventional insulin therapy on morbidity and mortality in patients with severe sepsis and septic shock (39). The study was terminated prematurely because of the significantly higher incidence of hypoglycemia (blood glucose <40 mg/dL) in patients randomized to receive intensive insulin therapy in comparison with conventional therapy (12.1% versus 2.1%, respectively; $P<0.001$) (38).

Rationale for Adjusting Rates of Insulin Infusion

The IIPs varied in dose adjustments. Some protocols adjusted the insulin infusion rate on the basis of only the measured blood glucose level, whereas others also took into account the patient's sensitivity to insulin.

In the Yale Protocol, the rate of insulin infusion was adjusted on the basis of the current blood glucose level, the previous value, and the current insulin infusion rate (23). Another protocol contained 5 different scales, each based on the expected severity of insulin resistance and the patient's sensitivity to the insulin (22). The Duke Protocol used a multiplier that takes into account the insulin sensitivity of patients (30). Other investigators made adjustments in their protocols based on the last 2 blood glucose measurements (17,27) or based on the blood glucose concentration and the concurrent insulin dosage (26).

The ACE recommends intravenous insulin protocols that take into account several factors, including the current and previous blood glucose levels and the current insulin infusion rate (36). It is suggested that algorithms that rely on a fixed relationship between insulin infusion rate and blood glucose levels cannot maintain the target glucose levels (32). Despite these recommendations, no clear evidence has demonstrated that one method of adjusting insulin infusions is more effective or safer than another method.

Methods of Blood Glucose Measurement

The published IIPs differed in the methods of blood glucose measurement and the types of blood samples used (Table 1). Glucose meters vary in their sensitivity and specificity, and the different types of blood samples yield varied results. The differences in the resulting glucose values may lead to clinical discrepancies regarding insulin dose titration.

In a prospective observational study, clinical agreement with the central laboratory was significantly better with arterial blood analysis (69.9% and 76.5% for glucose meter and blood gas/chemistry analysis, respectively) than with capillary blood analysis (56.8%; $P = 0.39$ and $P = 0.001$, respectively) (40). During hypoglycemia, clinical agreement was only 26.3% with capillary blood analysis and 55.6% and 64.9% for glucose meter and blood gas/chemistry analysis of arterial blood ($P = 0.010$ and $P<0.001$, respectively) (40). Glucose meter analysis of arterial and capillary blood samples tended to provide higher glucose measurements, whereas blood gas/chemistry analysis of arterial blood specimens tended to provide lower glucose values (40).

STRATEGIES TO IMPLEMENT IIPs SUCCESSFULLY

Introducing any new practice within an institution requires knowledge of sociopolitical, professional, intraprovider, patient, and practice-based factors that influence the adoption of guidelines (41). A multidisciplinary team is required to provide momentum for implementation of the protocol and to address issues and concerns of all disciplines involved in tight glucose control. In addition, gaining administrative support for implementing tight glycemic control is crucial to ensure that the efforts of the hospital staff are recognized and that any additional necessary resources are provided.

It is important to keep in mind that protocols must be adapted to each specific hospital environment and that no single protocol would be effective in all hospital settings (42). Furthermore, the insulin requirements in individual patients vary widely depending on various factors, such as insulin production reserves, insulin sensitivity, caloric intake, severity of illness, presence of infections, and use of certain medications such as corticosteroids (43). Therefore, any protocol should be viewed as a recommendation that may need to be adapted to the individual condition of each patient (43).

The ideal IIP should have sufficient details to achieve strict glucose control but should also be practical enough to be easily implemented by all ICU nurses. For example, the protocol recommended by Van den Berghe et al (2), which was associated with a significant improvement in morbidity and mortality, has been criticized for being difficult to implement in all ICUs. Intense and ongoing educational efforts are required for all involved disciplines to appreciate the value of tight glucose control in critically ill patients and to familiarize them with the IIP used by the hospital.

It is expected that even with the implementation of an IIP, not all patients will achieve glycemic control. Therefore, the presence of a diabetes consultation team is crucial for management of patients with hyperglycemia who are not adequately responding to the IIP or patients who are highly susceptible to hypoglycemia. A multidisciplinary team is ideal for addressing the various factors contributing to hyperglycemia and hypoglycemia in critically ill patients. In one study, a multidisciplinary diabetes team was associated with a decrease in duration of hospital stay in patients admitted to the medicine ward, in comparison with patients who did not receive a consultation or those who received a traditional individual endocrine consultation (44).

One major barrier to tight glycemic control is staff resistance to implementing protocols that necessitate increased workloads. IIPs require frequent monitoring of blood glucose levels and adjustments of insulin rates, which may be met with resistance by a busy ICU nursing staff. In one study, a standardized IIP significantly increased nursing workload (35% more glucose measurements were required), in comparison with the control cohort group (28). A gradual stepwise approach is recommended when introducing IIPs. At one medical center, each nursing unit was gradually transitioned until they became familiar with the new protocol, rather than introducing the new insulin protocol throughout the entire hospital at the same time (42). It took more than a year to introduce the protocol in all units, but this approach was associated with high satisfaction from both nurses and physicians (42). At another institution, an audit and feedback approach was used to facilitate the implementation of the IIP among nurses in intermediate care units, with a nurse-to-patient ratio of about 1:6 (45). Audits are objective measures of professional practice and patient outcomes, and feedback is the summary of clinical performance for a specified period. Intensive in-service education, an audit tool, and continuous constructive feedback to the nurses yielded positive results in implementing the IIP (45).

Another strong barrier to implementing an IIP is concern about occurrence of hypoglycemic events with use of tight glycemic control. All IIPs, however, require frequent glucose measurements and close monitoring of the patients to minimize the risk of hypoglycemia. The ideal frequency of blood glucose monitoring has not been studied. Most protocols require hourly monitoring of blood glucose levels until results are stable, at which point the frequency of measurements may be decreased.

The following have been identified as common sources of errors that may potentially result in hypoglycemia: lack of coordination between feeding and insulin administration, lack of sufficient frequency of blood glucose monitoring, orders not clearly written, and failure to recognize changes in insulin requirements because of certain conditions (for example, advanced age or renal failure) (46). Institutional protocols that address the management of mild, moderate, and severe hypoglycemia should be part of all IIPs, in order to achieve the maximal benefit of glycemic control while ensuring patient safety (36). With proper implementation of protocols and frequent monitoring of blood glucose, most cases of hypoglycemia are expected to be detected early and thus to be mild, transient, and not associated with adverse outcomes (36).

A recent retrospective cohort study (14) identified the following predisposing risk factors for hypoglycemia in critically ill patients: use of bicarbonate-based substitution fluid during venous hemofiltration, interruption in enteral or parenteral nutrition without adjustment of insulin infusion, prior diagnosis of diabetes mellitus, sepsis, inotropic support, and simultaneous use of insulin and octreotide. Therefore, under these conditions, the blood glucose levels may need to be assessed more frequently to avoid hypoglycemia.

A continuous improvement program should be implemented to analyze patterns in the process of care that are related to occurrence of hypoglycemia or hyperglycemia. Efforts to standardize clinical and documentation processes have been associated with a positive effect on the care of hospitalized patients with hyperglycemia (47). For prevention of incorrect constitution of intravenous insulin infusions, it is recommended that insulin infusions should be mixed in a uniform manner at a central location, preferably the pharmacy, and then sent to the nursing units (47). Another crucial factor is evaluation of the accuracy of the unit-based insulin glucose meters, especially in cases of extreme hematocrit levels (47). In addition, a protocol for blood glucose monitoring during diagnostic or therapeutic procedures is also recommended to minimize metabolic emergencies while the patient is off the medical floor undergoing a medical procedure (47).

The implemented IIP should be frequently assessed and modified, if needed, to meet the needs of the individual institution. Use of metrics to evaluate the success of the protocol helps to identify areas that promote the successful implementation of tight glycemic control.

The hospital equipment is also an important consideration when an IIP is developed for an institution. The infusion pump should be able to deliver accurately 0.1 U/h increments in the insulin infusion rate (32). Insulin infusions are generally prepared by mixing regular insulin with 0.9% saline in a 1-to-1 or 0.5-to-1 ratio (32).

CONCLUSION

Tight glycemic control is associated with decreased morbidity and mortality in critically ill patients. Intravenous insulin infusions are the recommended method to achieve glycemic control. The use of standardized protocols for insulin infusions is recommended to facilitate the achievement of tight glycemic control with minimal adverse outcomes and fluctuations.

When the available IIPs are reviewed, the situation in the ICU must be assessed to determine which protocol best meets the institution's needs. The optimal protocol should be based on the type of patients, the level of hyperglycemia in the critical care unit, the available resources, and the extent of acceptability of implementation of tight glycemic control.

DISCLOSURE

Dr. Moghissi is on the speakers' bureau for the following pharmaceutical companies: Abbott Laboratories, Amylin Pharmaceuticals, Inc., GlaxoSmithKline, Eli Lilly and Company, and Novo Nordisk Inc.

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