

CONVERSION OF INTRAVENOUS INSULIN INFUSIONS TO SUBCUTANEOUSLY ADMINISTERED INSULIN GLARGINE IN PATIENTS WITH HYPERGLYCEMIA

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ABSTRACT

Objective: To determine the optimal dose of insulin glargine needed to maintain glycemic control in patients undergoing conversion from intravenous regular insulin infusions to a subcutaneous insulin regimen.

Methods: Seventy-five hospitalized patients receiving continuous insulin infusions were randomized to receive 40%, 60%, or 80% of their total daily insulin requirement, calculated from the rate during the final 6 hours of the infusion, as insulin glargine at the time of conversion to a subcutaneous regimen. Prandial insulin aspart was added to the subcutaneous regimen when patients began oral intake, and the dosage was left to clinical judgment. Capillary blood glucose monitoring (CBGM) was performed before every meal and at bedtime. All CBGM values for the 24-hour period after conversion were collected.

Results: Three hundred ninety-two CBGM values were recorded and analyzed. The mean for all CBGM values during the 24-hour period after conversion to the subcutaneous insulin regimen was 151.9 ± 42.5 mg/dL in the 40% group, 164.0 ± 41.6 mg/dL in the 60% group, and 153.2 ± 66.2 mg/dL in the 80% group ($P = 0.66$). The percentage of CBGM values in the predefined study target range (80 to 140 mg/dL) was 43.2%, 34.8%, and 48% in the 40%, 60%, and 80% groups, respectively ($P = 0.09$). Secondary analysis with use of a glycemic target of 80 to 150 mg/dL and removal of outliers resulted in CBGM values within that range in 58.7%, 44.4%, and 67.6% for the 40%, 60%, and 80% groups, respectively (overall, $P = 0.001$; 40% group versus the 60% group, $P = 0.03$; 60%

group versus the 80% group, $P = 0.0004$; and 40% group versus the 80% group, $P = 0.18$).

Conclusion: Conversion from continuous insulin infusion to subcutaneously administered insulin glargine at a dose equal to 80% of the total daily insulin requirements resulted in the highest percentage of CBGM values in the glycemic target range of 80 to 150 mg/dL within the first 24 hours after regimen conversion in comparison with conversion at 40% and 60%, albeit the difference between the 40% and 80% groups was not statistically significant. (*Endocr Pract.* 2006;12:641-650)

Abbreviations:

BMI = body mass index; **CBGM** = capillary blood glucose monitoring; **ICU** = intensive care unit; **TPN** = total parenteral nutrition

INTRODUCTION

Diabetes mellitus is a major cause of morbidity and mortality. In the United States, approximately 20.8 million people have diabetes, a third of whom are unaware that they have the disorder (1). Hyperglycemia is common in hospitalized patients, with a prevalence of approximately 25%, and is an independent risk factor for a poor clinical outcome in numerous patient populations (2,3). Recent clinical trials have shown clear benefits relative to morbidity and mortality from intensive management of inpatient hyperglycemia, even in patients without a prior history of diabetes (4-8).

Critical illness is associated with an impairment of insulin secretion and insulin action, resulting in hyperglycemia even in normal subjects and a worsening of the hyperglycemia in patients with diabetes (9-14). In severe illness and other states of physical stress, hyperglycemia results from a myriad of factors. Increases in counterregulatory hormones, release of inflammatory cytokines, and accelerations in breakdown of fat and protein are detrimental and contribute to muscle wasting, poor wound healing, and an impaired ability to fight infection. In addition to stress-induced hyperglycemia, contributing factors to inpatient hyperglycemia include pharmacologic agents

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(15), enteral and total parenteral nutrition (TPN) (16,17), and glucocorticoid therapy (18).

In a recent Belgian study of critically ill patients with sepsis in the surgical intensive care unit (ICU) without a previous diagnosis of diabetes, the prevalence of hyperglycemia was 50% (4). Using a prospective, randomized, controlled design, Van den Berghe et al (4) showed that, in these patients, normalization of elevated glucose levels by intensive insulin therapy dramatically decreased in-hospital mortality and complication rates, specifically related to the incidence of sepsis, need for dialysis, blood transfusions, and polyneuropathy. In a similarly designed study in medical ICU patients, intensive insulin therapy diminished in-hospital mortality and complication rates, but it did not lead to a significant difference in ICU mortality (5). A recent meta-analysis of insulin therapy in critically ill hospitalized patients showed a 15% decrease in mortality in those receiving insulin therapy in comparison with control subjects (19). Postoperative hyperglycemia, especially during the first 24 to 48 hours, is associated with increased mortality and is an important predictor of serious postoperative infectious complications (20-22).

Continuous insulin infusion is an effective means of achieving and maintaining euglycemia. Practically, though, continuous insulin infusions are extremely labor-intensive and are infrequently used outside the ICU setting, even during the immediate postoperative period. Conversion from a continuous insulin infusion to a subcutaneous insulin regimen is common before transfer out of the ICU. Nevertheless, no conclusive data in the medical literature demonstrate the optimal method of conversion from a continuous insulin infusion to a subcutaneous insulin regimen that maintains euglycemia. The most physiologic subcutaneous insulin regimen includes a combination of long-acting basal insulin, such as insulin glargine (Lantus), and use of a rapid-acting insulin analogue for prandial insulin coverage and supplemental insulin to correct for hyperglycemia.

The primary objective of this study was to determine the optimal dose of insulin glargine necessary to maintain glycemic control in patients when treatment with intravenous regular insulin infusions is converted to a subcutaneous insulin regimen.

PATIENTS AND METHODS

Study Subjects

This prospective, randomized study was performed at Northwestern Memorial Hospital, a 776-bed tertiary care center in Chicago, Illinois, following the intention-to-treat principle. From August 2004 through May 2005, 75 patients with hyperglycemia were identified who required continuous insulin infusions in the cardiovascular and surgical ICUs and in the general medical and surgical wards. Patients gave informed consent for participation in the study under guidelines established by the Northwestern University Institutional Review Board. Inclusion criteria

simply required all study subjects to be receiving a continuous insulin infusion of regular insulin at the time of study entry. No exclusion criteria were used.

Study Procedures

Patients were randomized to receive 40%, 60%, or 80% of their total daily insulin requirement during continuous insulin infusion in the form of insulin glargine. The total daily insulin requirement was calculated in all patients, including those in whom the continuous insulin infusion had been administered for less than 24 hours, by averaging the insulin infusion rates for the 6 hours preceding the conversion (to obtain an hourly rate that provided glycemic control) and then multiplying the result by 24 hours. The continuous insulin infusion was discontinued 2 hours after the glargine dose was administered. Prandial insulin aspart (NovoLog) was added to the subcutaneous regimen when patients began oral intake, and the dosage was left to clinical judgment. Capillary blood glucose monitoring (CBGM) was performed before every meal and at bedtime in those tolerating an oral diet, every 6 hours if the patient was receiving nothing by mouth or continuous enteral nutrition or TPN, and with greater frequency as clinically indicated for 24 hours after conversion to the subcutaneous insulin regimen. Supplemental short-acting insulin was administered to 1 patient receiving continuous tube feedings and rapid-acting insulin was administered to the other 74 patients when blood glucose levels exceeded 150 mg/dL. The target glycemic range for patients receiving the subcutaneous regimen was defined as blood glucose levels from 80 to 140 mg/dL. Protocol adherence, with regard to correct administration of basal, prandial, and supplemental insulin, was monitored.

For each patient, demographic data were collected including age, sex, weight, height, body mass index (BMI), length of stay in the ICU, duration of stay in the hospital, history of impaired glucose tolerance, history of diabetes mellitus, history of diabetic retinopathy, nephropathy, or neuropathy, history of tobacco use, and any additional comorbidities. Prehospital and inpatient medications were screened for oral hypoglycemic agents and insulin as well as medications and substances known to alter insulin sensitivity or secretion—specifically, vasopressors, corticosteroids, TPN, or immunosuppressive agents.

All CBGM values for the 24-hour monitoring period were collected. Glucose values were analyzed at times 0, 6, 12, and 24 hours (relative to administration of the first dose of insulin glargine) and for the first fasting glucose levels the morning after conversion of the insulin regimen. Hypoglycemic events (defined as blood glucose values <50 mg/dL) with or without symptoms and hyperglycemic events (defined as blood glucose values >200 mg/dL) were recorded. Complications that occurred during the duration of the patient's hospitalization, including infections, acute renal failure, respiratory failure, need for blood transfusion, need for reoperation, and death, were recorded.

Statistical Analysis

Statistical analysis was performed with one-way analysis of variance (and use of the Tukey test on all statistically significant results) by using GraphPad InStat version 3.00 for Windows 95 (GraphPad Software, San Diego, CA). The number of CBGM values in each glucose range was analyzed by a χ^2 test for independence, and a Fisher exact test was performed on statistically significant results to assess intergroup statistically significant differences. For this study, *P* values less than 0.05 were considered statistically significant.

RESULTS

The study population consisted of 56 men and 19 women, including 26 patients previously diagnosed with diabetes (25 with type 2 diabetes and 1 with type 1 diabetes) and 1 with impaired fasting glucose (Table 1). Of the overall study cohort, 51 patients had recently undergone a cardiovascular surgical procedure, and 72 were in the ICU at study initiation. The mean age of the 75 patients was 60.2 ± 11.7 years, mean weight was 90.1 ± 19.4 kg, and mean BMI was 29.8 ± 6.6 kg/m². Sixty patients (80%) were overweight (BMI >25 kg/m²), and 29 (39%) were obese (BMI >30 kg/m²). Medical histories were significant for coronary artery disease in 36 study subjects (48%), hypertension in 56 (75%), hypercholesterolemia in 50 (67%), and renal disease in 10 (13%). Six patients (8%) either had a history of organ transplantation or had just undergone organ transplantation before the onset of the study. With the exception of the number of obese subjects (more in the 60% group) and a disproportionately high number of patients with transplantation randomized to the 80% group, the study population was evenly distributed. The immunosuppressive regimen for organ transplantation involved large doses of glucocorticoids with a rapid tapering, generally 50% per day. These large doses of corticosteroids contributed to severe hyperglycemia.

Protocol adherence was monitored to verify appropriate basal, prandial, and supplemental insulin administration as ordered. Overall compliance with study protocol was 83%, with prandial insulin was 88%, and with supplemental insulin was 93% (data not shown) and did not differ between groups.

Outliers

Six patients had clinical events or study protocol violations during the first 24 hours after conversion from intravenous insulin infusion to the subcutaneous insulin regimen that either prevented sufficient CBGM to be done or significantly affected their glycemic control. In one patient (in the 60% group) with a history of renal transplantation and coronary artery bypass grafting, acute renal failure developed on the day of insulin conversion. Treatment was initiated with stress-dose corticosteroids for allograft rejection during the monitoring period, lead-

ing to severe hyperglycemia. One patient with a history of type 2 diabetes and liver transplantation underwent tracheal stent placement and was started on stress-dose corticosteroids concurrent with insulin conversion. This patient (in the 80% group) received an extra dose of NPH insulin during the monitoring period for management of severe hyperglycemia. Other protocol violations included 1 patient with incomplete glucose monitoring (in the 40% group) and 3 patients who received doses of insulin glargine different from the calculated dose based on randomization (1 in the 40% group and 2 in the 80% group). Because this is an intention-to-treat study, we included all data collected in the analysis except when specified in the following material.

Insulin Infusion Rates

The mean insulin infusion rates 6 hours before conversion to the subcutaneous regimen differed among the 3 groups, despite randomization, with the 40% group requiring 2.1 ± 1.0 U/h, the 60% group requiring 2.9 ± 1.4 U/h, and the 80% group requiring 3.0 ± 1.6 U/h (*P* = 0.044) (Table 2). Baseline glucose levels at the time of conversion from continuous insulin infusion were 138.2 ± 36.3 mg/dL (for the 40% group), 133.6 ± 29.5 mg/dL (for the 60% group), and 116.2 ± 30.3 mg/dL (for the 80% group) (*P* = 0.0445); thus, those receiving higher insulin infusion rates had lower glucose values. The total daily insulin requirements during insulin infusion for the 24 hours before conversion of the treatment regimen were not statistically different despite the variation in glycemic control. Thus, the conversion factor (40%, 60%, or 80%) for the insulin glargine dose administered remains a valid primary study variable.

Glucose Values

From all 75 study participants, 392 capillary blood glucose measurements were recorded and analyzed (Table 3). The only patient to have a hypoglycemic event (defined as a glucose value <50 mg/dL) was in the 40% group, whereas 25 study subjects had at least one hyperglycemic measurement (defined as a glucose value >200 mg/dL) within the first 24 hours after regimen conversion. Of the patients with hyperglycemia, 11 were in the 60% group in comparison with only 7 in each of the other groups.

The mean for all CBGM values during the 24-hour monitoring period after conversion to subcutaneous administration of insulin was 151.9 ± 42.5 mg/dL in the 40% group, 164.0 ± 41.6 mg/dL in the 60% group, and 153.2 ± 66.2 mg/dL in the 80% group (Table 4). Despite the aforementioned statistically significant difference in baseline glucose, all 3 groups had increases in mean glucose levels at 6 hours, with values that were not significantly different (Fig. 1). At 6 hours after regimen conversion, those in the 40% group had a mean glucose level of 157.2 ± 47.2 mg/dL, in comparison with 159.7 ± 43.9 mg/dL for those in the 60% group and 166.2 ± 72.4

Table 1
Baseline Characteristics of 75 Patients With Hyperglycemia
Receiving Continuous Insulin Infusion, Overall and Stratified by Insulin Dosage*

Factor	All (N = 75)	40% group (N = 25)	60% group (N = 25)	80% group (N = 25)	P value
Age (yr)	60.2 ± 11.7	61.4 ± 13.7	60.7 ± 10.8	58.6 ± 10.2	0.68
Sex (male:female)	56:19	20:5	18:7	18:7	
Weight (kg)	90.1 ± 19.4	88.7 ± 16.3	91.0 ± 21.2	90.6 ± 20.3	0.90
BMI (kg/m ²)	29.8 ± 6.6	28.9 ± 5.0	30.6 ± 6.4	29.9 ± 8.0	0.66
Impaired glucose tolerance	1	0	1	0	0.36
History of diabetes	26	8	10	8	0.79
Duration (yr)	9.1	8.1	8.4	10.8	
History of retinopathy	4	2	0	2	0.35
History of nephropathy	5	1	2	2	0.80
History of neuropathy	4	1	2	1	0.77
Oral hypoglycemic medication	13	4	6	3	0.52
Insulin at admission	12	4	4	4	1.00
Past medical history of:					
Coronary artery disease	36	11	12	13	0.85
Hypertension	56	16	21	19	0.26
Hypercholesterolemia	50	16	16	18	0.79
Peripheral vascular disease	9	2	4	3	0.68
Cerebrovascular accident	8	2	2	4	0.57
Overweight (BMI >25 kg/m ²)	60	20	20	20	1.00
Obese (BMI >30 kg/m ²)	29	8	12	9	0.48
History of smoking	45	15	13	17	0.51
Current smokers	10	4	1	5	0.22
Transplantation	6	1	1	4	0.19
Corticosteroids at admission	5	2	2	1	0.80
Tacrolimus at admission	3	1	1	1	1.00
Renal disease	10	4	2	4	0.80
Dialysis-dependent patients	2	0	1	1	0.77

*BMI = body mass index. Numbers denote number of patients unless indicated otherwise.

mg/dL for those in the 80% group. At 12 hours after regimen conversion, those in the 80% group had the lowest mean glucose level (153.2 ± 77.9 mg/dL) and those in the 60% group had the highest mean glucose value (165.6 ± 57.0 mg/dL). At the end of the study period, 24 hours after conversion from continuous insulin infusion to subcutaneously administered insulin, the 40% and 80% groups were similar, with mean glucose levels of 151.6 ± 44.5 mg/dL and 152.9 ± 65.1 mg/dL, respectively, while the 60% group had an insignificantly higher mean glucose level (163.0 ± 59.8 mg/dL). The first morning glucose level after conversion to insulin glargine was the lowest in the 80% group (144.6 ± 70.8 mg/dL) in comparison with the values for the 40% and 60% groups of 154.0 ± 54.4

mg/dL and 155.7 ± 43.6 mg/dL, respectively. The percentage of CBGM values in the predefined study target range (80 to 140 mg/dL) was 43.2% in the 40% group, 34.8% in the 60% group, and 48% in the 80% group ($P = 0.09$) (Fig. 2).

Although 80 to 140 mg/dL was the predefined glycemic target in our study and differences among the 3 insulin dosage groups were not significant, we also performed an analysis using the range of 80 to 150 mg/dL, which has been deemed by some investigators to be the optimal glycemic target range for the non-ICU setting and the use of subcutaneously administered insulin (6). The CBGM values were within the range of 80 to 150 mg/dL 61.6% of the time in the 80% group, in comparison with

Table 2
Continuous Insulin Infusion Data
for the Overall Study Group and Stratified by Insulin Dosage

Factor	All (N = 75)	40% group (N = 25)	60% group (N = 25)	80% group (N = 25)	P value
Pre-insulin infusion glucose (mg/dL)	198.8 ± 58.6	187.6 ± 61.9	210.0 ± 59.6	198.7 ± 51.6	0.40
Duration receiving insulin infusion (h)	34.5 ± 40.0	33.3 ± 26.2	43.9 ± 59.4	26.5 ± 22.6	0.30
Peak insulin infusion rate (U/h)	4.8 ± 2.3	4.3 ± 2.0	5.3 ± 2.4	4.7 ± 2.41	0.28
Duration of infusion overlap (h)	1.5 ± 1.3	1.5 ± 1.2	1.34 ± 1.2	1.7 ± 1.48	0.57
Mean insulin infusion rate for 6 h before conversion (U/h)	2.7 ± 1.4	2.1 ± 1.0	2.9 ± 1.4	3.0 ± 1.6	0.044
Preconversion glucose level (mg/dL)	129.7 ± 33.5	138.2 ± 36.3	133.6 ± 29.5	116.2 ± 30.3	0.045
Mean glargine dose administered (U/mL)	40.7 ± 27.7	22.5 ± 19.2	41.3 ± 19.7	57.6 ± 30.4	
Prandial insulin ordered	32 (43%)	14 (56%)	12 (48%)	6 (24%)	0.059

only 56.0% of the time in the 40% group and 41.5% of the time in the 60% group (Fig. 2) (overall, $P = 0.0034$; 40% group versus the 60% group, $P = 0.02$; 60% group versus the 80% group, $P = 0.0013$; and 40% group versus the 80% group, $P = 0.378$).

Removal of data from the aforementioned patients who had protocol violations (2 in the 40% group, 1 in the 60% group, and 3 in the 80% group) revealed improvement in glycemic trends across all cohorts, but the data for the 80% group were the most affected (Table 5). The mean baseline glucose levels were no longer significantly different between groups. In the 80% group, mean glucose levels for the entire 24-hour period of monitoring decreased from 153.2 ± 66.2 mg/dL to 140.9 ± 27.7 mg/dL, with similar trends evident at each monitored

interval. Furthermore, the mean first morning glucose level declined from 144.6 ± 70.8 mg/dL to 128.6 ± 25.9 mg/dL in the 80% group with these outliers removed. Thus, the glycemic control in the 40% and 80% groups, although previously noted as similar, now differed under these circumstances, and the difference among all groups approached statistical significance (overall, $P = 0.0688$; 40% group versus the 80% group, $P = 0.0858$). After removal of the outliers, the percentages of CBGM values in the range of 80 to 150 mg/dL improved even more—58.7%, 44.4%, and 67.6% for the 40%, 60%, and 80% groups, respectively (overall, $P = 0.001$; 40% group versus the 60% group, $P = 0.0319$; 60% group versus the 80% group, $P = 0.0004$; and 40% group versus the 80% group, $P = 0.1791$).

Table 3
Capillary Blood Glucose Monitoring Values (N = 392),
Stratified by Insulin Dosage and Glycemic Range

Glucose range (mg/dL)	40% group (N = 132)		60% group (N = 135)		80% group (N = 125)		P value
	No.	%	No.	%	No.	%	
<50	1	0.8	0	0	0	0	0.3526
50-70	0	0	2	1.5	5	4.0	0.0506
71-80	1	0.8	1	0.7	2	1.6	0.7369
81-110	13	9.8	8	5.9	16	12.8	0.1631
111-120	13	9.8	11	8.1	10	8.0	0.8400
121-140	31	23.5	28	20.7	34	27.2	0.4717
141-150	17	12.9	9	6.7	17	13.6	0.1396
151-180	31	23.5	30	22.2	18	14.4	0.1465
>180	25	18.9	46	34.1	23	18.4	0.0032

Table 4
Results of 24-Hour Blood Glucose Monitoring After Conversion From Intravenous Infusion to Subcutaneous Administration of Insulin, Stratified by Insulin Dosage

Mean glucose level (mg/dL)	40% group (N = 25)	60% group (N = 25)	80% group (N = 25)	P value
At time 0	138.2 ± 36.3	133.6 ± 29.5	116.2 ± 30.3	0.0445
At 6 hours	157.2 ± 47.2	159.7 ± 43.9	166.2 ± 72.4	0.8419
At 12 hours	157.7 ± 47.1	165.6 ± 57.0	153.2 ± 77.9	0.6850
At 24 hours	151.6 ± 44.5	163.0 ± 59.8	152.9 ± 65.1	0.7436
First AM	154.0 ± 54.4	155.7 ± 43.6	144.6 ± 70.8	0.7631
Mean of all glucose levels 24 hours after glargine dose	151.9 ± 42.5	164.0 ± 41.6	153.2 ± 66.2	0.6578

DISCUSSION

This study showed no statistically significant differences in glycemic control for conversion from a continuous insulin infusion to a subcutaneous insulin regimen by using 40%, 60%, or 80% of the total daily intravenous insulin requirements as basal insulin according to a primary intention-to-treat analysis that used a target glucose range of 80 to 140 mg/dL. Secondary analyses with use of the more generally accepted target range of 80 to 150 mg/dL, however, showed remarkable differences between the groups, with the trend being that the 80% group had better glycemic control and more CBGM values within the glycemic target range. Furthermore, when the patients who had significant protocol violations were excluded from analysis and the glycemic target range of 80 to 150

mg/dL was used, the lower mean glucose levels in the 80% group became even more apparent. In addition, the data provide insight into other variables that affect glycemic control during the first 24 hours after conversion from an insulin infusion.

The American College of Endocrinology Task Force on Inpatient Diabetes and Metabolic Control recommends intensive glycemic control (glucose levels of 80 to 110 mg/dL) in the ICU setting and further suggests fasting glucose values <110 mg/dL and maximal glucose values <180 mg/dL in non-ICU areas (23). Conversion from continuous insulin infusion to multiple daily injections of insulin glargine has been previously studied in the outpatient setting but not the inpatient setting (24). In that study, glycemic control was achieved with the administration of insulin glargine in a dose equivalent to the amount of total

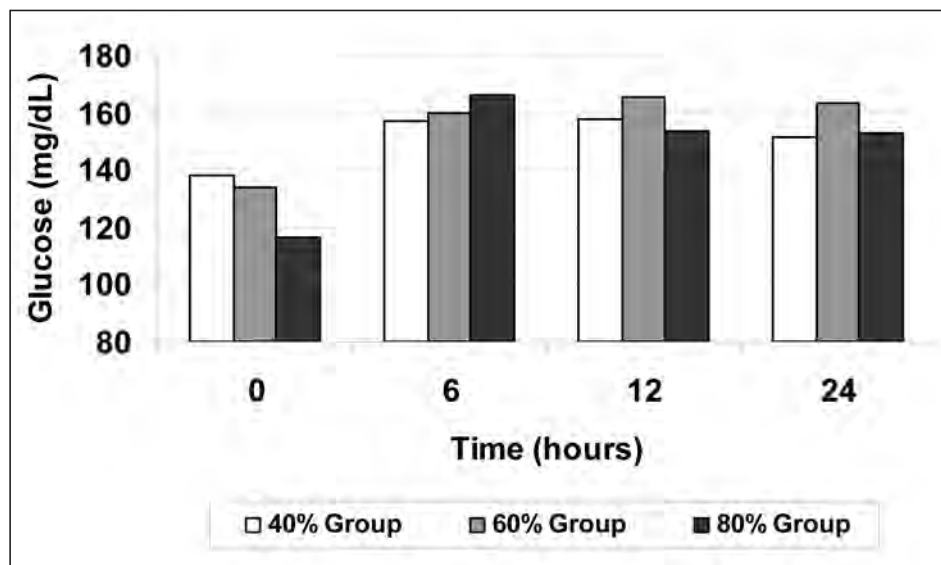


Fig. 1. Results of blood glucose monitoring in 75 study subjects, stratified by dosage group, during 24-hour period after conversion from intravenous insulin infusion to subcutaneous administration of insulin glargine.

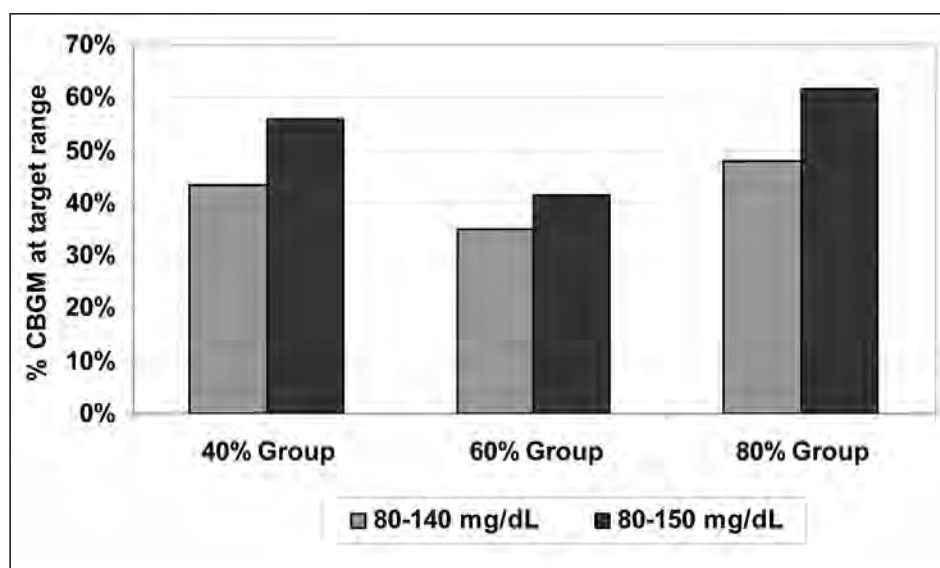


Fig. 2. Percentage of all capillary blood glucose monitoring (CBGM) values within target ranges during 24-hour period after conversion from intravenous insulin infusion to subcutaneous administration of insulin glargine, stratified by dosage group.

basal insulin administered by means of continuous subcutaneous insulin infusion. In our study, conversion to basal insulin at a dose equal to 80% of a patient's total daily insulin requirement resulted in CBGM values within our study target range of 80 to 140 mg/dL 48% of the time, between 80 and 150 mg/dL more than half the time (61.6%), and in the range of 80 to 180 mg/dL the vast majority of the time (76%; this value increased to 83.8% when the outliers were removed).

Hypoglycemia, defined as a glucose level <50 mg/dL, was almost nonexistent in our study and occurred in only 1 patient from the 40% group. After removal of the CBGM measurements from a single patient who had received twice the amount of insulin glargine as ordered, a glucose level ≤ 70 mg/dL was encountered only 8 times (2%); thus, a reassuring safety profile emerged, even for an 80% conversion factor. Preexisting renal insufficiency, defined as stage 3 chronic kidney disease or worse (glomerular filtration rate <60 mL/min per 1.73 m²), was present in 13% of our patients, but no increased rate of hypoglycemia was noted in these patients (data not shown). Although the medical literature lacks formal studies of insulin glargine clearance in patients with renal dysfunction, requirements for insulin glargine (like other insulins) may be diminished because of reduced insulin metabolism.

Before performance of our current study, we predicted a linear relationship between glycemic control and the conversion factor used. Surprisingly, our data were nonlinear, an indication of failure of the randomization process. The best glycemic control occurred in the patients in the 80% conversion group, followed by the 40% group. Despite randomization, the study participants in the 60% dosage conversion group had the longest duration of insulin infusion before regimen conversion, the longest

length of stay in the ICU, the highest peak insulin infusion rate, the highest infection rate, the highest blood transfusion rate, and the highest incidence of reoperation and rehospitalization within 30 days after dismissal from the hospital (data not shown) in comparison with the 2 other study groups. Thus, the 60% group overall had more severe illness. Most likely, a larger sample size would have reduced confounding variability in severity of illness across cohorts. In addition to the foregoing, the insulin infusion rate immediately before conversion to the insulin glargine regimen was significantly lower in the 40% group than in the other 2 study groups, a finding that implies a substantially lower degree of insulin resistance. This factor may also partially explain the relative similarity of results in the 40% and 80% groups. Despite a diverse cohort, we did not perform subgroup analysis on patients with type 2 diabetes separately. Recent data in patients who had undergone a cardiothoracic surgical procedure suggest that levels of insulin resistance are similar during the immediate postoperative period in patients with type 2 diabetes and those with stress-induced hyperglycemia (25).

Achieving a high level of glycemic control in hospitalized patients is not accomplished without some practical problems, many of which were not foreseen. Standardized protocols for both continuous insulin infusion and subcutaneous administration of insulin had been used at our institution for more than 12 months at the time of initiation of our study (26). Nursing staffs in the ICU and non-ICU settings had undergone insulin protocol in-service training and were familiar with the order sets; accordingly, hyperglycemia could be promptly treated without additional clinician intervention. Within the first 6 hours after conversion to the subcutaneous insulin regimen, however, we found a notable increase in glucose

Table 5
Results of 24-Hour Blood Glucose Monitoring After Conversion
From Intravenous Infusion to Subcutaneous Administration of Insulin,
Stratified by Insulin Dosage After Removal of Outliers

Mean glucose level (mg/dL)	40% group (N = 23)	60% group (N = 24)	80% group (N = 22)	P value
At time 0	132.1 ± 30.8	129.5 ± 22.7	115.0 ± 29.1	0.0881
At 6 hours	152.0 ± 44.5	157.0 ± 43.0	152.5 ± 31.5	0.8987
At 12 hours	143.3 ± 24.6	157.1 ± 39.6	140.5 ± 30.9	0.1805
At 24 hours	145.5 ± 34.7	153.9 ± 40.8	143.5 ± 39.1	0.6164
First AM	145.6 ± 37.6	153.7 ± 43.3	128.6 ± 25.9	0.0688
Mean of all glucose levels 24 hours after glargine dose	145.4 ± 29.9	158.2 ± 31.2	140.9 ± 27.7	0.1256

levels. One attributable factor in this worsening of glycemic control was an insufficient duration of overlap of the insulin infusion with the insulin glargine dose. Data from Lepore et al (27) have shown the time of onset of action for insulin glargine to be 1.5 hours, but the full effect on glycemic control is not evident until 4 hours after administration. Review of medical records revealed variable adherence with the overlap period of the insulin infusion after administration of insulin glargine, especially if a transfer out of the ICU occurred concomitantly with conversion of the insulin regimen. How much this overlap nonadherence accounts for differences seen between the study groups in glucose levels 6 hours after administration of insulin glargine cannot be determined. Regimen conversion in conjunction with concurrent administration of insulin glargine and a rapid-acting insulin analogue may provide adequate coverage and eliminate the need for an overlap period altogether. Practically speaking, removal of the overlap period potentially eliminates infusion discontinuation errors and may hasten transfer out of the ICU.

This study focused on basal insulin as the primary variable of glycemic control during the first 24 hours after conversion from a continuous insulin infusion regimen. Most of our study subjects were in the postoperative period and not eating while receiving the continuous insulin infusion. Often, consumption of a clear liquid diet with high glucose foods (mainly juices) was initiated concurrently with conversion from the intravenous to the subcutaneous insulin regimen and was unaccounted (and uncontrolled) for in the study design. Prandial insulin, an important component of intensive insulin management, was not controlled in our study, and dosing was left to the clinical judgment of the managing clinician. As noted in Table 2, prandial insulin was used in approximately half the patients in the 40% and 60% groups and in only 24% of the study subjects in the 80% group. Furthermore, patients with nausea who were unsure they would tolerate oral intake may have had prandial insulin withheld despite

eating a meal. These limitations in study design could have affected our outcomes and contributed to higher glucose values. Thus, our data do not show any statistically significant results between groups.

On the basis of the glycemic control and safety profile shown in this study, the Glucose Management Service at our institution has altered our insulin conversion strategy. Similar to the study protocol, the insulin infusion rate is used as a guide to determine total daily insulin requirements, averaged for the preceding 6 hours to obtain an hourly rate that provides glycemic control. The mean infusion rate is multiplied by 24 hours to calculate the total daily insulin requirement. The basal insulin dose ordered is 80% of the total daily insulin requirement and usually administered as a once-daily subcutaneous injection of insulin glargine. A conversion dose of rapid-acting insulin of 10% of the initial insulin glargine dose is concomitantly administered with the initial insulin glargine dose at separate injection sites, concurrent with the discontinuation of the intravenous insulin drip. The prandial insulin dose ordered for each meal is 10% of the glargine dose, usually given as insulin aspart per the hospital formulary. This dose is somewhat less than that generally recommended because the patients are eating only small amounts (usually only clear liquids) at this point. Following the initial 24 hours after conversion to subcutaneously administered insulin, the basal insulin dose is routinely reduced—as long as the patient does not have clinically significant hyperglycemia. Subsequent glargine doses are similarly adjusted downward as the insulin resistance attributable to the surgical stress lessens. In contrast, however, the same amount of prandial insulin is continued for the duration of the hospitalization because the patient's oral intake usually improves during this period. CBGM is performed before every meal and at bedtime in those patients tolerating an oral diet, every 6 hours in those receiving nothing by mouth or continuous enteral nutrition or TPN, and with greater frequency as clinically indicated.

Supplemental short-acting or rapid-acting insulin is administered when blood glucose levels exceed 150 mg/dL.

CONCLUSION

In this investigation, conversion from a continuous insulin infusion to subcutaneously administered insulin glargine equal to 80% of the total daily insulin requirements resulted in the highest percentage of CBGM values in the glycemic target range of 80 to 150 mg/dL within the first 24 hours after regimen conversion in comparison with conversion at 40% and 60%, albeit the difference between the 40% and 80% groups was not statistically significant. Our study investigated only the initial 24-hour period after conversion from a continuous insulin infusion to a subcutaneous insulin regimen. Additional studies are needed to assess strategies for inpatient subcutaneous insulin titration, especially in the nondiabetic population, and to show outcome benefits of glycemic control in the non-ICU setting.

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DISCLOSURE

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REFERENCES

1. **Centers for Disease Control and Prevention.** National diabetes fact sheet: general information and national estimates on diabetes in the United States, 2005. Rev ed. Atlanta, GA: U.S. Department of Health and Human Services, Centers for Disease Control and Prevention, 2005. Available at: <http://www.cdc.gov/DIABETES/pubs/factsheet.htm>. Accessed for verification June 11, 2006.
2. **Umpierrez GE, Isaacs SD, Bazargan N, You X, Thaler LM, Kitabchi AE.** Hyperglycemia: an independent marker of in-hospital mortality in patients with undiagnosed diabetes. *J Clin Endocrinol Metab.* 2002;87:978-982.
3. **Capes SE, Hunt D, Malmberg K, Pathak P, Gerstein HC.** Stress hyperglycemia and prognosis of stroke in non-

- diabetic and diabetic patients: a systematic overview. *Stroke.* 2001;32:2426-2432.
4. **Van den Berghe G, Wouters P, Weekers F, et al.** Intensive insulin therapy in critically ill patients. *N Engl J Med.* 2001;345:1359-1367.
5. **Van den Berghe G, Wilmer A, Hermans G, et al.** Intensive insulin therapy in the medical ICU. *N Engl J Med.* 2006;354:449-461.
6. **Furnary AP, Wu Y, Bookin SO.** Effect of hyperglycemia and continuous intravenous insulin infusions on outcomes of cardiac surgical procedures: the Portland Diabetic Project. *Endocr Pract.* 2004;10(Suppl 2):21-33.
7. **Wahab NN, Cowden EA, Pearce NJ, Gardner MJ, Merry H, Cox JL (ICONS Investigators).** Is blood glucose an independent predictor of mortality in acute myocardial infarction in the thrombolytic era? *J Am Coll Cardiol.* 2002;40:1748-1754.
8. **Guvener M, Pasaoglu I, Demircin M, Oc M.** Perioperative hyperglycemia is a strong correlate of postoperative infection in type II diabetic patients after coronary artery bypass grafting. *Endocr J.* 2002;49:531-537.
9. **Klonoff DC, Schwartz DM.** An economic analysis of interventions for diabetes. *Diabetes Care.* 2000;23:390-404.
10. **Vasa FR, Molitch ME.** Endocrine problems in the chronically critically ill patient. *Clin Chest Med.* 2001;22:193-208.
11. **Lind L, Lithell H.** Impaired glucose and lipid metabolism seen in intensive care patients is related to severity of illness and survival. *Clin Intensive Care.* 1994;5:100-105.
12. **Wolfe RR.** Substrate utilization/insulin resistance in sepsis/trauma. *Baillieres Clin Endocrinol Metab.* 1997;11:645-657.
13. **Chambrier C, Laville M, Rhzioual Berrada K, Odeon M, Bouletreau P, Beylot M.** Insulin sensitivity of glucose and fat metabolism in severe sepsis. *Clin Sci (Lond).* 2000;99:321-328.
14. **McCowen KC, Malhotra A, Bistrrian BR.** Stress-induced hyperglycemia. *Crit Care Clin.* 2001;17:107-124.
15. **Luna B, Feinglos MN.** Drug-induced hyperglycemia. *JAMA.* 2001;286:1945-1948.
16. **Rosmarin DK, Wardlaw GM, Mirtallo J.** Hyperglycemia associated with high, continuous infusion rates of total parenteral nutrition dextrose. *Nutr Clin Pract.* 1996;11:151-156.
17. **Cheung NW, Napier B, Zaccaria C, Fletcher JP.** Hyperglycemia is associated with adverse outcomes in patients receiving total parenteral nutrition. *Diabetes Care.* 2005;28:2367-2371.
18. **Hollingdal M, Juhl CB, Dall R, et al.** Glucocorticoid induced insulin resistance impairs basal but not glucose entrained high-frequency insulin pulsatility in humans. *Diabetologia.* 2002;45:49-55.
19. **Pittas AG, Siegel RD, Lau J.** Insulin therapy for critically ill hospitalized patients: a meta-analysis of randomized controlled trials. *Arch Intern Med.* 2004;164:2005-2011.
20. **Pomposelli JJ, Baxter JK III, Babineau TJ, et al.** Early postoperative glucose control predicts nosocomial infection rate in diabetic patients. *JPEN J Parenter Enteral Nutr.* 1998;22:77-81.
21. **Furnary AP, Zerr KJ, Grunkemeier GL, Heller AC.** Hyperglycemia: a predictor of mortality following CABG in diabetics. *Circulation.* 1999;100(Suppl):1591.
22. **Zerr KJ, Furnary AP, Grunkemeier GL, Bookin S, Kanhere V, Starr A.** Glucose control lowers the risk of wound infection in diabetics after open heart operations. *Ann Thorac Surg.* 1997;63:356-361.

23. American College of Endocrinology position statement on inpatient diabetes and metabolic control. *Endocr Pract.* 2004;10:77-82.
24. **Bode BW, Steed RD, Schleusener DS, Strange P.** Switch to multiple daily injections with insulin glargine and insulin lispro from continuous subcutaneous insulin infusion with insulin lispro: a randomized, open-label study using a continuous glucose monitoring system. *Endocr Pract.* 2005;11:157-164.
25. **Liao P, DeSantis A, Schmeltz L, et al.** Insulin resistance following cardiothoracic surgery with and without a preoperative diagnosis of type 2 diabetes during treatment with intravenous insulin therapy for postoperative hyperglycemia. Abstract presented at: 66th Annual American Diabetes Association Scientific Conference, June 9-13, 2006, Washington, DC. Abstract #420P. Available at: <http://scientificsessions.diabetes.org/index.cfm?fuseaction=Locator.DisplaySearchAbstract&CalledBYID=1006>. Accessed for verification June 11, 2006.
26. **DeSantis AJ, Schmeltz LR, Schmidt K, et al.** Inpatient management of hyperglycemia: the Northwestern experience. *Endocr Pract.* 2006;12:491-505.
27. **Lepore M, Pampanelli S, Fanelli C, et al.** Pharmacokinetics and pharmacodynamics of subcutaneous injection of long-acting human insulin analog glargine, NPH insulin, and Ultralente human insulin and continuous subcutaneous infusion of insulin lispro. *Diabetes.* 2000; 49:2142-2148.