Insulin Therapy and Glycemic Control in Hospitalized Patients With Diabetes During Enteral Nutrition Therapy

A randomized controlled clinical trial

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OBJECTIVE — To compare two subcutaneous insulin strategies for glycemic management of hyperglycemia in non–critically ill hospitalized patients with diabetes during enteral nutrition therapy (ENT).

RESEARCH DESIGN AND METHODS — Fifty inpatients were prospectively randomized to receive sliding-scale regular insulin (SSRI) alone ($n = 25$) or in combination with insulin glargine ($n = 25$). NPH insulin was added for persistent hyperglycemia in the SSRI group (glucose >10 mmol/l).

RESULTS — Glycemic control was similar in the SSRI and glargine groups (mean ± SD study glucose 8.9 ± 1.6 vs. 9.2 ± 1.6 mmol/l, respectively; $P = 0.71$). NPH insulin was added in 48% of the SSRI group subjects. There were no group differences in frequency of hypoglycemia (1.3 ± 4.1 vs. 1.1 ± 1.8%; $P = 0.35$), total adverse events, or length of stay.

CONCLUSIONS — Both insulin strategies (SSRI with the addition of NPH for persistent hyperglycemia and glargine) demonstrated similar efficacy and safety in non–critically ill hospitalized patients with type 2 diabetes during ENT.

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H yperglycemia is a commonly encountered complication of inpatient enteral nutrition therapy (ENT) (1,2). In one study, 34% of subjects receiving ENT experienced blood glucose levels >11.1 mmol/l (2). This degree of hyperglycemia is associated with adverse patient outcomes and prolonged hospital length of stay (LOS) (3–5).

Although several subcutaneous insulin regimens are proposed for managing patients during ENT in noncritical care units, there are no studies comparing these strategies (4). This results in the pre-scribing of insulin therapy according to clinician preference often without achieving desired glycemic targets (6,7).

The primary aim of this study was to compare the effect of administration of sliding-scale regular insulin (SSRI) alone with that of administration of insulin glargine in combination with SSRI on glycemic control, adverse events, and hospital LOS during inpatient ENT.

RESEARCH DESIGN AND METHODS — This open-label, randomized clinical trial was approved by

the institutional review board. All patients provided written consent.

Fifty inpatients meeting criteria for inpatient diagnosis of diabetes with two or more blood glucose measures >7.2 mmol/l during ENT were randomized to the SSRI ($n = 25$) or glargine ($n = 25$) groups. The SSRI was administered every 4–6 h according to results of bedside glucose monitoring (LifeScan, Milpitas, CA) using a previously published regimen (8) (see Appendix A in the online appendix available at http://care.diabetesjournals.org/cgi/content/full/dc08-1436/DC1). Patients who were able to eat during ENT had glucose monitoring and SSRI timed before meals and bedtime.

The goal in both groups was to achieve glucose levels between 5.6 and 10 mmol/l while avoiding hypoglycemia. Bedside glucose results were reviewed on a daily basis by one of the investigators, who adjusted insulin therapy according to prespecified algorithms (see online appendices B and C). NPH insulin was added in the SSRI group for persistent glucose levels >10 mmol/l. Hypoglycemia (glucose <3.9 mmol/l) was treated according to a previously published guideline (9) and prompted decreases in frequency or intensity of SSRI or basal insulin. Glucose results are presented as overall study mean, daily mean, mean peak, and nadir values. Each subject had a maximum of six glucose values per 24 h. When more than one glucose value was measured in a 4-h interval, the maximum or minimum value defined that time period.

Additional data collected included insulin type and dose, morning triglycerides at randomization and study completion, ENT formula and delivery rate, severity-of-illness scores (10), Charlson score (11), adverse events (Table 1), and LOS. Hypoglycemia frequency is reported as percentage of patient-days with one or more event and percentage of all glucose values <3.9 mmol/l.

Statistical analyses were performed using SAS (version 9.1). The intention-to-

See accompanying editorial, p. 751.

Table 1—*Clinical data for glargine and SSRI groups*

	Glargine	SSRI	*P*
n	25	25	
Age (years)	67 ± 10	63 ± 10	0.20
Sex (female)	36	44	0.56
BMI (kg/m^2)	29.1 ± 5.8	26.9 ± 1.7	0.22
Previous diabetes	11 (44)	14 (56)	0.40
LOS (days)	24.2 ± 18.2	23.8 ± 18.8	0.85
Severity-of-illness score	110 ± 25	105 ± 24	0.27
Charlson score	4.9 ± 3.3	3.6 ± 3.4	0.17
Primary diagnosis			
GI cancer/mass	13	13	
Esophageal tear/rupture	3	1	
Pancreatitis	1	3	
Head and neck cancer	2	1	
Other	6	7	
Glycemic data			
Entry glucose (mmol/l)	9.8 ± 2.7	9.9 ± 2.7	
Study day 1	9.6 ± 2.3	9.6 ± 2.5	0.59
Study day 2	9.7 ± 2.6	9.2 ± 2.3	0.52
Study day 3	9.6 ± 2.3	9.2 ± 2.4	0.57
Study day 4	9.4 ± 2.1	9.3 ± 2.4	0.98
Study day 5	8.8 ± 1.8	9.1 ± 1.9	0.66
Study day 6	8.6 ± 1.4	8.4 ± 1.6	0.62
Study day 7	8.8 ± 1.8	7.8 ± 1.3	0.27
Study day 8	7.8 ± 1.8	8.0 ± 1.4	0.48
Mean study glucose (mmol/l)	9.1 ± 1.6	8.9 ± 1.6	0.71
Mean peak glucose (mmol/l)	11.4 ± 2.7	11.5 ± 2.9	0.95
Mean nadir glucose (mmol/l)	6.9 ± 1.6	6.7 ± 1.2	0.51
Hypoglycemia			
Patient days	2.7	4.8	0.34
Blood glucose measures	1.3	1.1	0.35
Insulin			
Total daily dose (units)	27.2 ± 20.5	27.0 ± 28.5	0.33
SSRI (units/day)	11.3 ± 9.3	15.7 ± 12.4	0.22
Total daily dose (units · kg^{-1} · day^{-1})	0.33 ± 0.26	0.33 ± 0.33	
Basal insulin (%)	66.9 ± 13.8	24.0 ± 28.7	0.001
NPH and SSRI (%)*	NA	55.1 ± 7.0	0.45†
Triglycerides (mmol/l)			
Baseline	1.6 ± 0.5	1.6 ± 0.8	0.52
End of study	1.6 ± 0.5	1.6 ± 0.5	0.95
Adverse events (*n*)			
Body temperature >100.4°F (days)	0	8	0.003
Antibiotic use (days)	64	74	0.13
Arrythmias	1	2	1.0
Pulmonary emboli	2	1	0.49
Deep venous thrombosis	2	0	1.0
Wound infection	1	0	
Respiratory symptoms	2	2	1.0
Cardiac arrest	0	1	1.0
Liver abscess	1	0	1.0

Data are percent, *n* (%), or means ± SD unless otherwise indicated. *$n = 12$. †Compared with the glargine group. GI, gastrointestinal; NA, not available.

treat principle was used for group comparisons of continuous data with Student's *t* test or Wilcoxon's rank-sum test and of categorical data with the χ^2 or Fisher's exact test. Paired Student's *t* tests were performed to compare within-group differences.

RESULTS — The clinical data for each group are summarized in Table 1. The mean duration of participation was 6.0 ± 2.2 days (range 1–8) in both groups. No group differences were observed in glycemic measures or triglycerides during the study (Table 1).

Twelve patients in the SSRI group required the continuation ($n = 2$) or addition ($n = 10$; days 2–5) of NPH insulin. These patients had higher baseline glucose levels (11.3 ± 3.1 vs. 8.5 ± 1.4 mmol/l; $P = 0.011$) and severity-of-illness scores (115 ± 20 vs. 96 ± 24; $P = 0.04$), required more insulin (47 ± 29 vs. 9 ± 10 units/day; $P < 0.01$), and were more likely to have diabetes preceding admission (67 vs. 46% in the glargine group). Total daily insulin doses were similar between the SSRI and glargine groups (Table 1).

Decisions regarding type of ENT formula were made by the primary team and nutrition service. Several patients received more than one type of ENT formula during this study, with variation in the percentage of carbohydrate calories (34–65%). The majority of patients ($n = 29$) received formulations containing ≥50% carbohydrate. With the exception of more days with a body temperature >100.4°F in the SSRI group, there were no differences in adverse events (Table 1).

CONCLUSIONS — This is the first randomized study comparing subcutaneous insulin regimens in non–critically ill inpatients with diabetes receiving ENT. Similar levels of glycemic control were achieved in each group, suggesting that early addition of basal insulin with careful attention to glycemic control is effective and safe in these patients.

The level of glycemic control achieved in this study is similar to that achieved in a prior report where subcutaneous insulin doses were based on an initial dose-finding regimen with intravenous insulin in patients receiving ENT (12). Although intravenous insulin may offer advantages of rapid attainment of glycemic control during dose-defining periods, many hospitals do not permit this on general nursing units. In addition, the rate and duration of ENT can change frequently, requiring ongoing adjustments in scheduled insulin (13).

Concern for hypoglycemia with basal insulin in patients receiving ENT contributes to an overdependence on SSRI regimens (6). Although SSRI was effective in some patients in this and previous reports, any missed dose can result in hyperglycemia (14,15). The subjects who

continued SSRI alone in this study had lower glucose levels at randomization and were less likely to have preadmission diabetes. Administration of an SSRI may, thus, be a reasonable initial strategy for selected patients receiving ENT; however, it is important to initiate scheduled insulin once glucose levels exceed 10 mmol/l (7).

This study has important implications for clinical practice. More than 50% of study patients had no prior history of diabetes, underscoring the importance of monitoring glucose levels with ENT initiation to allow identification of those requiring insulin (3). These findings provide a guide for insulin therapy in inpatients who develop hyperglycemia during ENT.

The small number of patients is an important limitation to widespread application of this study. Although the glycemic control achieved was not optimal, frequent changes in the rate and type of ENT were contributing factors. Patients receiving ENT spend the majority of time in a postprandial state, with altering recommendations for glycemic control (4,7). Studies that investigate strategies for safely achieving specified glycemic targets during ENT in larger numbers of patients are needed.

In conclusion, we demonstrated that the majority of non–critically ill inpatients will require basal insulin during ENT to achieve and maintain a reasonable degree of glucose control. Although SSRI may be an acceptable initial therapy in the setting of mild hyperglycemia or in patients without prior diabetes, scheduled insulin is required once a consistent insulin requirement is demonstrated.

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