Efficacy of Subcutaneous Insulin Lispro versus Continuous Intravenous Regular Insulin for the Treatment of Patients with Diabetic Ketoacidosis

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PURPOSE: To compare the efficacy and safety of subcutaneous insulin lispro with that of a standard low-dose intravenous infusion protocol of regular insulin in patients with uncomplicated diabetic ketoacidosis.

METHODS: In this prospective, randomized open trial, 20 patients treated with subcutaneous insulin lispro were managed in regular medicine wards (n = 10) or an intermediate care unit (n = 10), while 20 patients treated with the intravenous protocol were managed in the intensive care unit. Patients treated with subcutaneous lispro received an initial injection of 0.3 unit/kg followed by 0.1 unit/kg/h until correction of hyperglycemia (blood glucose levels <250 mg/dL), followed by 0.05 to 0.1 unit/kg/h until resolution of diabetic ketoacidosis (pH ≥7.3, bicarbonate ≥18 mEq/L). Patients treated with intravenous regular insulin received an initial bolus of 0.1 unit/kg, followed by an infusion of 0.1 unit/kg/h until correction of hyperglycemia, then 0.05 to 0.1 unit/kg/h until resolution of diabetic ketoacidosis.

RESULTS: Mean (± SD) admission biochemical parameters in patients treated with subcutaneous lispro (glucose: 674 ± 154 mg/dL; bicarbonate: 9.2 ± 4 mEq/L; pH: 7.17 ± 0.10) were similar to values in patients treated with intravenous insulin (glucose: 611 ± 264 mg/dL; bicarbonate: 10.6 ± 4 mEq/L; pH: 7.19 ± 0.08). The duration of treatment until correction of hyperglycemia (7 ± 3 hours vs. 7 ± 2 hours) and resolution of ketoacidosis (10 ± 3 hours vs. 11 ± 4 hours) in patients treated with subcutaneous lispro was not different than in patients treated with intravenous regular insulin. There were no deaths in either group, and there were no differences in the length of hospital stay, amount of insulin until resolution of diabetic ketoacidosis, or in the rate of hypoglycemia between treatment groups. Treatment of diabetic ketoacidosis in the intensive care unit was associated with 39% higher hospitalization charges than was treatment with subcutaneous lispro in a non–intensive care setting ($14,429 ± $5243 vs. $8801 ± $5549, $P < 0.01$).

CONCLUSION: Treatment of adult patients who have uncomplicated diabetic ketoacidosis with subcutaneous lispro every hour in a non–intensive care setting may be safe and more cost-effective than treatment with intravenous regular insulin in the intensive care unit. **Am J Med. 2004;117:291–296.**

The mainstay in the treatment of patients with diabetic ketoacidosis involves the administration of low doses of regular insulin by continuous intravenous infusion or by frequent subcutaneous or intramuscular injections (1–4). Although controlled studies have shown that low-dose insulin therapy is effective regardless of the route of administration (3,4), intravenous administration is commonly preferred because of the potential delay in the onset of action and the longer half-life of subcutaneous regular insulin (5–7). One study reported that intravenous regular insulin led to a more rapid decrease in plasma glucose and ketone levels in the first 2 hours than did intramuscular or subcutaneous insulin (3). However, in 30% to 40% of patients treated with intramuscular or subcutaneous insulin, plasma glucose levels were lowered by less than 10% in the first hour of therapy. This delay in the onset of action was also substantiated in another study involving frequent small subcutaneous injections, in which only 4 of 24 patients showed a decrease in glucose concentration in the first 3 hours (8). In the majority of medical centers in the United States, treatment involving intravenous insulin infusion requires admission to the intensive care unit because of the intensity of treatment or the institutional policies that prevent the use of intravenous insulin outside the intensive care setting (9–12). Admission to the intensive care unit has been associated with more testing and higher hospitalization costs in patients with diabetic ketoacidosis (9,13).

Recently, new analogs of human insulin that have a rapid

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Table 1. Treatment Protocol for Diabetic Ketoacidosis

Intravenous fluids
- 0.9% saline at 500 to 1000 mL/h for 2 hours
- 0.45% saline at 250 to 500 mL/h until blood glucose levels <250 mg/dL (13.9 mmol/L)
- Dextrose 5% in 0.45% saline at 150 to 250 mL/h until resolution of diabetic ketoacidosis

Potassium replacement
- If serum K^+ levels >5.5 mEq/L, do not give K^+ but check serum levels every 2 hours
- K^+ levels = 4 to 5.5 mEq/L, add 20 mmol of KCl to each liter of intravenous fluid
- K^+ levels = 3 to <4 mEq/L, add 40 mmol of KCl to each liter of intravenous fluid
- K^+ levels = <3 mEq/L, give 10 to 20 mmol of KCl per hour until serum levels >3 mEq/L, then add 40 mmol of KCl to each liter of intravenous fluid

Insulin therapy

Subcutaneous lispro every hour
- Initial dose subcutaneously: 0.3 unit/kg of body weight, followed by
- Subcutaneous lispro insulin at 0.1 unit/kg/h
- When blood glucose levels <250 mg/dL, change intravenous fluids to dextrose 5% in 0.45% saline and reduce rate to 0.05 unit/kg/h to keep glucose levels ~200 mg/dL (11.1 mmol/L) until resolution of diabetic ketoacidosis

Intravenous regular insulin
- a) Initial intravenous bolus: 0.1 unit/kg body weight, followed by
- b) Continuous insulin infusion at 0.1 unit/kg/h
- When blood glucose levels <250 mg/dL, change intravenous fluids to dextrose 5% in 0.45% saline and reduce rate to 0.05 unit/kg/h to keep glucose levels ~200 mg/dL (11.1 mmol/L) until resolution of diabetic ketoacidosis

Laboratory
- Admission: cell blood count with differential, complete metabolic profile, venous pH, and serum β-hydroxybutyrate
- During treatment: basic metabolic profile (glucose, bicarbonate, potassium, chloride, urea, and creatinine), venous pH, phosphorus, and β-hydroxybutyrate at 2 hours, 4 hours, and every 4 hours until resolution of diabetic ketoacidosis
- Glucose by finger stick: check glucose every hour in patients receiving hourly insulin lispro injections and every 2 hours in patients receiving intravenous insulin

onset of action—insulin lispro (Humalog; Eli Lilly & Co, Indianapolis, Indiana) and aspart insulin (Novolog; Novo Nordisk, Princeton, New Jersey)—have become available and may represent alternatives to the use of regular insulin in the treatment of patients with diabetic ketoacidosis. Subcutaneous administration of insulin analogs (14) has an onset of action within 10 to 20 minutes, a peak within 30 to 90 minutes, and a duration of action of approximately 3 to 4 hours, which is shorter than with regular insulin that has an onset of action of 1 to 2 hours and a half-life of about 4 hours (1,15). The aim of this prospective, randomized study was to compare the efficacy and safety of subcutaneous insulin lispro with that of low-dose continuous intravenous regular insulin in the treatment of patients with uncomplicated diabetic ketoacidosis.

METHODS

The sample comprised 40 patients with diabetic ketoacidosis who were recruited from the Atlanta Medical Center and the University of Tennessee Health Science Center. The research protocol was approved by the institutional review boards at both institutions. The diagnosis of diabetic ketoacidosis was established in the emergency department using a plasma glucose level >250 mg/dL (13.9 mmol/L), a serum bicarbonate level <15 mEq/L, a blood pH <7.3, a positive serum ketone level at a dilution ≥1:4 by the nitroprusside reaction, and a serum β-hydroxybutyrate level >31 mg/dL (>3 mmol/L). We excluded patients who had persistent hypotension (systolic blood pressure <80 mm Hg) after the administration of 1 liter of normal saline, comatose state (loss of consciousness), acute myocardial ischemia, heart failure, end-stage renal disease, anasarca, dementia, or pregnancy.

Patients were assigned in the emergency department to receive subcutaneous insulin lispro or intravenous regular insulin following a computer-generated randomization table. Due to hospital regulations disallowing the use of intravenous insulin outside the intensive care unit, patients treated with intravenous insulin were admitted to the intensive care unit, while patients treated with subcutaneous lispro were managed on a general medicine floor or in a step-down unit. Patients were managed by members of the internal medicine residency program, who received a copy of the assigned treatment protocol (Table 1).

Patients assigned to continuous intravenous regular insulin received an initial bolus of 0.1 unit/kg, followed by a continuous infusion of regular insulin calculated to deliver 0.1 unit/kg/h until blood glucose levels decreased to approximately 250 mg/dL (13.9 mmol/L). At this time, intravenous

Table 2. Biochemical Profile on Admission

Characteristic	Subcutaneous Insulin Lispro (n = 20)	Intravenous Regular Insulin (n = 20)	*P* Value
	Mean ± SD or Number (%)		
Age (years)	37 ± 12	39 ± 14	0.50
Male sex	12 (60)	13 (65)	
Duration of diabetes (years)	6.7 ± 5	6.9 ± 4	
African American	15 (75)	16 (80)	
Body mass index (kg/m^2)	26 ± 7	27 ± 9	0.60
Glucose* (mg/dL)	674 ± 154	611 ± 264	0.36
Bicarbonate (mEq/L)	9.2 ± 4	10.6 ± 4	0.99
Venous pH	7.17 ± 0.10	7.19 ± 0.08	0.36
β-hydroxybutyrate† (mmol/L)	9.9 ± 4	8.0 ± 3	0.89
Free fatty acids‡ (mmol/L)	2.0 ± 0.9	2.4 ± 0.6	0.57

* To convert mg/dL to mmol/L, multiply by 0.0555.
† To convert mmol/L to mg/dL, divide by 0.09605.
‡ To convert mmol/L to mg/dL, divide by 0.03906.

fluids were changed to dextrose-containing solutions, and the insulin infusion rate was decreased to 0.05 unit/kg/h until resolution of diabetic ketoacidosis.

Patients assigned to subcutaneous lispro insulin received an initial injection of 0.3 unit/kg of body weight, followed by 0.1 unit/kg/h until blood glucose levels reached 250 mg/dL. The insulin dose was then reduced to 0.05 unit/kg/h, and the intravenous fluids were changed to dextrose 5% in 0.45% normal saline to keep blood glucose at a level of about 200 mg/dL (11.1 mmol/L) until resolution of diabetic ketoacidosis.

Ketoacidosis was considered resolved when serum bicarbonate levels were ≥18 mEq/L and venous pH was >7.3 (2). When these occurred, intravenous insulin infusion or subcutaneous lispro was discontinued 1 hour after the administration of patients" maintenance dose of regular and intermediate-acting insulin. Patients with newly diagnosed diabetes received an initial insulin dose of 0.6 unit/kg of body weight per day; two thirds in the morning and one third in the evening.

During treatment, blood glucose levels were determined at bedside by fingerstick every 2 hours in patients treated with intravenous regular insulin and every hour in those who received hourly injections of subcutaneous lispro. Levels of glucose, electrolytes, phosphorus, venous pH, β-hydroxybutyrate, free fatty acids, and insulin were measured on admission before the initiation of insulin and at 4, 6, 8, 12, 16, and 24 hours after treatment. Medical care data included site of admission and treatment in the hospital, amount of fluid and insulin administration, and length of hospitalization. Response to medical therapy (the primary outcome measurement) was evaluated by assessing the time required for resolution of hyperglycemia and ketoacidosis, and the rate of hypoglycemia during insulin infusion. Hypoglycemia was defined as a blood glucose value ≤60 mg/dL (3.3 mmol/L).

Plasma glucose levels were measured using the glucose oxidase method. Serum β-hydroxybutyrate levels were determined by a standard enzymatic method. Serum free fatty acid levels were measured using a colorimetric method established in our laboratory (16).

Statistical Analysis

Comparison of continuous variables was carried out using the unpaired *t* test, and the Mann-Whitney *U* test when data were skewed. For comparison of categorical variables, chi-squared analyses were performed. We arbitrarily estimated a difference between groups of ≥5 hours to determine ketoacidosis as being clinically important. A sample size of 20 patients was needed in each group to provide a power of 0.93, given an α level of 0.05, an SD of 4, and a 1:1 inclusion ratio. The value for standard deviation used in the power calculation is a conservative estimate based on previous reports (10). Statistical significance was defined as a type 1 error of 0.05. Stat View, version 5.0 (SAS Institute, Cary, North Carolina), and PS: Power and Sample Size version (Vanderbilt Medical Center, Nashville, Tennessee), were used for the statistical analysis and sample size calculations.

RESULTS

The 20 patients treated with subcutaneous insulin lispro were managed in regular medicine wards (n = 10) or in a step-down unit (n = 10), whereas the 20 patients who received an intravenous infusion of regular insulin were admitted to the intensive care unit. The mean age and duration of diabetes were similar between the two treat-

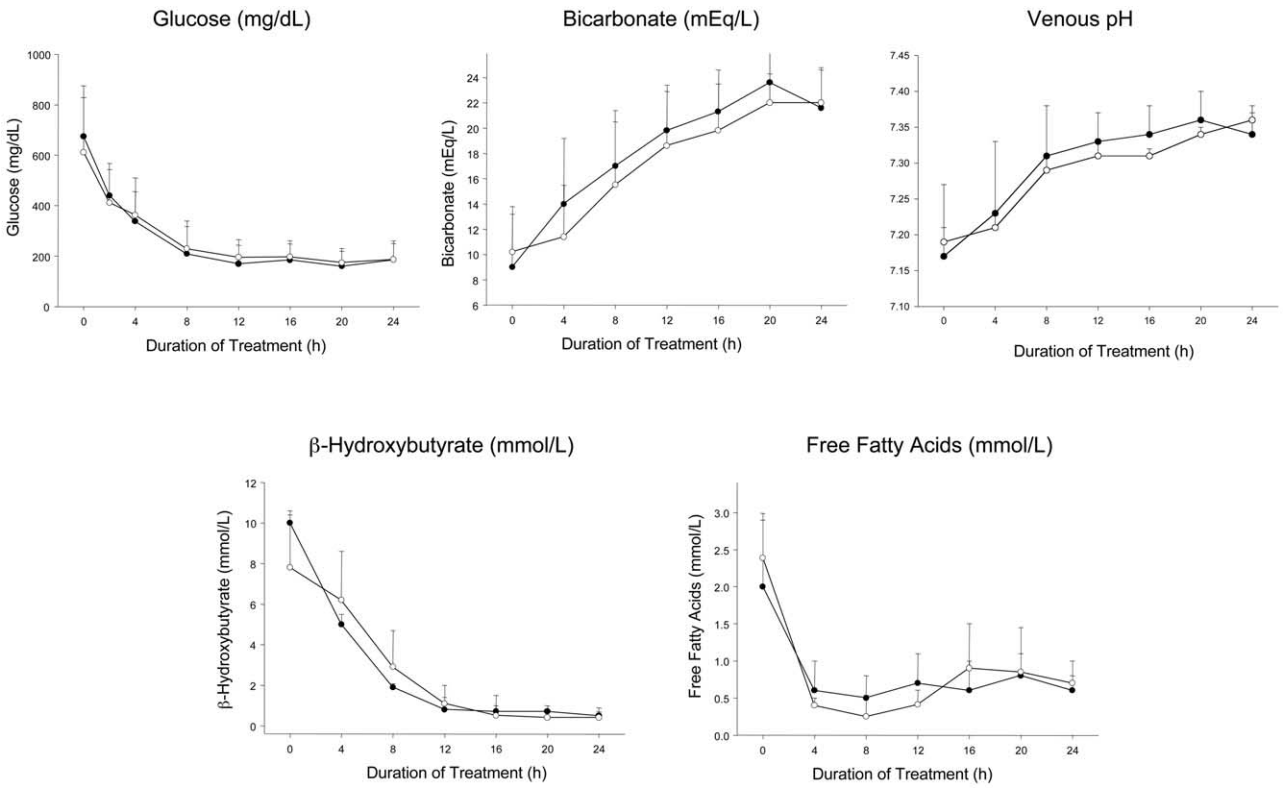

Figure. Changes in the metabolic profile of patients with diabetic ketoacidosis who were treated with subcutaneous insulin lispro every hour (open circles) or continuous intravenous regular insulin (filled circles). Circles represent means, and error bars represent SD. To convert β-hydroxybutyrate from mmol/L to mg/dL, divide by 0.09605. To convert free fatty acid from mmol/L to mg/dL, divide by 0.03906.

ment groups (Table 2). The precipitating cause of diabetic ketoacidosis was also similar between the two groups; poor compliance with therapy was the cause in 60% of patients treated with subcutaneous lispro and in 70% of those treated with intravenous regular insulin. Three patients (15%) were diagnosed as having diabetes upon hospital admission.

Admission biochemical parameters in patients treated with subcutaneous lispro were similar to those in subjects treated with intravenous insulin (Table 2). There were no differences in admission concentration or in the rate of decline in plasma glucose levels, or in the correction of acid-base parameters, during treatment (Figure).

There were no deaths in either treatment group, and there were no differences in the length of hospital stay or amount of insulin administered until resolution of ketoacidosis between the two groups (Table 3). Likewise, the mean duration of treatment until glucose concentration reached $<$250 mg/dL and the duration of treatment until resolution of ketoacidosis were not different between the two groups of patients. None of the patients had recurrence of ketoacidosis. One patient in each treatment group experienced mild hypoglycemia. One patient in the intravenous insulin group had a plasma glucose level of 54 mg/dL (3 mmol/L) 8 hours after treatment, whereas another patient who was treated with subcutaneous lispro had a blood glucose level of 55 mg/dL (3.1 mmol/L) 12 hours after treatment.

Treatment of diabetic ketoacidosis in a non–intensive care setting (step-down unit or general medicine ward) was associated with a 39% lower hospitalization charge than was treatment with intravenous regular insulin in the intensive care unit ($8801 $\pm$ $5549 [range, $5342 to $22,320] vs. $14,429 $\pm$ $5243 [range, $2605 to $20,314], $P < 0.01$). The average hospitalization charges per day was $3981 $\pm$ $1067 for patients treated in an intensive care unit compared with $2682 $\pm$ $636 for those treated in a non–intensive care setting.

DISCUSSION

The aim of this study was to compare the efficacy of subcutaneous insulin lispro with that of a standard low-dose intravenous infusion of regular insulin in patients with uncomplicated diabetic ketoacidosis. Our results indicate that treatment with subcutaneous insulin lispro in general medicine wards or in an intermediate-care unit is as safe and effective as treatment with intravenous regular insulin in the intensive care unit. The rate of decline of

Table 3. Response to Medical Treatment in Patients with Mild or Moderate Diabetic Ketoacidosis

Variable	Subcutaneous Insulin Lispro	Intravenous Regular Insulin	*P* Value
	Mean ± SD or Number (%)		
Hospital stay (days)	4 ± 2	4 ± 1	0.14
Duration of treatment until resolution of hyperglycemia (days)	7 ± 3	7 ± 2	0.29
Duration of therapy until resolution of diabetic ketoacidosis (hours)	10 ± 3	11 ± 4	0.87
Amount of insulin until resolution of diabetic ketoacidosis (units)	84 ± 32	98 ± 26	0.22
Episodes of hypoglycemia during therapy	1 (5)	1 (5)	
Recurrence of diabetic ketoacidosis	0	0	

blood glucose concentration and the duration of treatment until resolution of ketoacidosis were similar between the two treatment groups. By avoiding admission to the intensive care unit, however, the use of subcutaneous insulin lispro resulted in lower hospitalization charges than did intravenous regular insulin treatment in an intensive care setting.

Until 1972, large doses of insulin were used in the treatment of patients with diabetic ketoacidosis (17–19). Complicated schemes were available for the selection of initial and subsequent insulin dosage according to the degree of hyperglycemia and ketonemia. Large doses of insulin, up to 100 units/h or more given intravenously, subcutaneously, or intramuscularly, were thought to be necessary to prevent insulin resistance (19). However, since the pioneering work of Sonksen et al in 1972 (20), the use of low-dose regular insulin by continuous intravenous infusion (21) or by intramuscular (1,22,23) or subcutaneous (3,24) injection has been shown to be as effective as higher doses of insulin and has become the standard of care. The appeal of low-dose insulin comes from the ease of administration and its appeal on physiological grounds (1,23,25,26). Furthermore, substantial reductions in the rate of hypokalemia and hypoglycemia have been demonstrated with low-dose protocols in both adults and children with diabetic ketoacidosis (23,25,27,28). The rate of absorption of regular insulin administered intramuscularly or subcutaneously are comparable (3), and both regimens have been shown to be equally effective as intravenous infusion in resolving hyperglycemia and acidosis. Most diabetologists, however, prefer the use of intravenous infusion because of concerns about delayed absorption of subcutaneous regular insulin in the presence of hypovolemia and impaired tissue perfusion (5–7).

Cost control without compromising the overall quality of care should be a priority in the present environment of escalating medical expenditure and managed care. Care in the intensive care unit has been associated with more testing and considerably higher hospitalization costs in patients with diabetic ketoacidosis (9,13), which is in agreement with our findings. Our results indicate that treatment in a non–intensive care setting was associated with a 39% lower hospitalization charge, with an average difference of about $5600 per case, a value similar to that previously reported for patients with diabetic ketoacidosis (9,29).

In urban and medically indigent populations, poor compliance with insulin treatment represents the most common precipitating cause of diabetic ketoacidosis, accounting for more than half of all diabetic ketoacidosis admissions (6,30–33). Most patients who are noncompliant are younger and less critically ill, and have lower mortality, as compared with nondiabetic ketoacidosis patients admitted to the intensive care unit (10). In patients with mild or moderate disease, the length of hospital stay, in-hospital mortality rate, and time to resolution of ketoacidosis have been shown to be independent of treatment in the intensive care setting (9,34,35). Still, despite the lack of benefits in treating diabetic ketoacidosis in the intensive care unit as compared with in step-down units or regular medicine wards, patients with diabetic ketoacidosis in the United States are frequently admitted to the intensive care unit (9,11,12,29,30). Our study indicates that management in the intensive care setting is not necessary for successful treatment of uncomplicated diabetic ketoacidosis, and that treatment with subcutaneous insulin lispro in medicine wards or step-down units is as safe and effective.

Our study has several limitations. The sample was small and excluded patients with hypovolemic shock, comatose state, acute myocardial ischemia, heart failure, end-stage renal disease, anasarca, or pregnancy. Although the treatment protocol was well accepted by residents and nursing staff, and there were no reported irregularities in adherence to the protocol, hourly insulin injections may have been difficult to administer in some instances owing to the intensity of treatment and shortage of nursing staff on regular wards. However, restrictions on the intensity of nursing care in the institutions in

our study are consistent with the nursing care available in general hospitals in the southeast United States (30).

Our results indicate that in adult patients with uncomplicated diabetic ketoacidosis, treatment with subcutaneous lispro insulin in a non–intensive care setting is safe and more cost-effective than treatment with intravenous regular insulin in the intensive care unit. In agreement with previous reports (9,10,29), our study indicates that the current practice of admitting all patients with diabetic ketoacidosis to the intensive care unit should be discouraged. We believe that such admission should not be dictated by the severity of hyperglycemia or metabolic acidosis, but by the severity of intercurrent medical illness that led to metabolic decompensation. Based on our results, we conclude that patients with uncomplicated diabetic ketoacidosis should be treated with rapid-acting analogs in a non–intensive care setting.

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