

Subcutaneous Insulin Lispro Is Safe and Cost-Effective for Diabetic Ketoacidosis

Umpierrez GE, Latif K, Stoeber J, et al. Efficacy of subcutaneous insulin lispro versus continuous intravenous regular insulin for the treatment of patients with diabetic ketoacidosis. *Am J Med* 2004;117:291–6.

Study Overview

Objective. To compare the efficacy and safety of subcutaneous insulin lispro to that of intravenous (IV) regular insulin in patients with uncomplicated diabetic ketoacidosis.

Design. Prospective, randomized, open-label trial.

Setting and participants. Patients were recruited from 1 of 2 U.S. medical centers. Patients were eligible to participate if they were diagnosed with diabetic ketoacidosis in the emergency department of the 2 study institutions. Diagnostic criteria for diabetic ketoacidosis included plasma glucose level > 250 mg/dL, serum bicarbonate level < 15 mEq/L, a blood pH < 7.3, a positive serum ketone level at a dilution \geq 1:4 by nitroprusside reaction, and a serum β -hydroxybutyrate level > 31 mg/dL. Patients with persistent hypotension (systolic blood pressures < 88 mm Hg) after administration of 1 L of normal saline, comatose patients, pregnant patients, and patients with heart failure, acute myocardial infarctions, end-stage renal disease, anasarca, or dementia were excluded.

Intervention. Patients were randomized to either the intervention group (subcutaneous insulin lispro) or standard care group (IV regular insulin). In both hospitals, any patient allocated to IV regular insulin was admitted to the intensive care unit (ICU) per hospital policy. Patients randomized to insulin lispro were managed on either a general medicine floor or a step-down unit, based on their provider's discretion. Patients assigned to subcutaneous insulin lispro were managed with an initial injection of 0.3 U/kg followed by 0.1 U/kg per hour until blood glucose levels reached 250 mg/dL. At this time, the insulin dose was reduced to 0.05 U/kg per hour and dextrose-containing solutions were given until resolution of ketoacidosis. Patients allocated to continuous IV regular insulin received an initial bolus of 0.1 U/kg followed by a continuous infusion of 0.1 U/kg per hour of regular insulin until blood glucose levels were reduced to 250 mg/dL. At this time, the insulin infusion was decreased to 0.05 U/kg per hour and dextrose-containing solutions were given until resolution of diabetic ketoacidosis.

Main outcome measures. Time to resolution of hyperglycemia and ketoacidosis. Ketoacidosis was considered resolved when a serum bicarbonate level of \geq 18 mEq/L and blood pH of > 7.3 was reached. During the treatment period, blood glucose levels were measured every 2 hours for patients allocated to the standard care group and every hour for patients in the intervention group. Secondary outcome was the rate of hypoglycemia during the insulin infusions. Hypoglycemia was defined as a blood glucose level of \leq 60 mg/dL.

Main results. Twenty patients were randomized to subcutaneous insulin lispro and 20 to continuous IV regular insulin infusion. Half of the patients allocated to the intervention group were managed in regular medicine wards, while the remaining patients were managed in a step-down unit. All 20 patients allocated to the standard therapy group were managed in the ICU. Baseline characteristics and biochemical parameters were similar between the 2 groups. No differences in outcome means were seen between the subcutaneous insulin lispro or the IV regular insulin groups in either hospital stay (4 days versus 4 days; $P = 0.14$), duration of treatment until resolution of hyperglycemia (7 days versus 7 days; $P = 0.29$), duration of therapy until resolution of diabetic ketoacidosis (10 hours versus 11 hours; $P = 0.87$), amount of insulin until resolution of ketoacidosis (84 U versus 98 U; $P = 0.22$), episodes of hypoglycemia (each group with 1), and recurrence of diabetic ketoacidosis occurring in neither group). Hospital charges were significantly lower for the intervention group compared with the standard care group (\$8801 versus \$14,429; $P < 0.01$).

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Conclusion. Treatment with subcutaneous insulin lispro is similar in efficacy to treatment with continuous regular insulin infusions in adult patients with uncomplicated diabetic ketoacidosis. This strategy may be cost-effective in some settings.

Commentary

Diabetic ketoacidosis is a potentially life-threatening condition that requires emergent management. The current standard of care for diabetic ketoacidosis involves continuous IV infusions of low doses of regular insulin [1,2]. Because of the intense monitoring associated with IV insulin therapy, many centers in the United States have institutional policies in place that require patients on IV insulin to be managed within an ICU [3]. Despite evidence to suggest that patients with mild to moderate diabetic ketoacidosis may be adequately managed in a non-ICU setting [4], many patients are still routinely admitted to the ICU for management.

In this randomized, open-label trial, patients were allocated to either treatment with subcutaneous insulin lispro in a non-ICU setting or management with continuous IV regular insulin in the ICU. Patient care outcomes were similar between the groups, while, not surprisingly, hospital charges were almost 40% greater for patients randomized to standard care. This study adds to the growing body of literature suggesting that a strategy of admitting all diabetic ketoacidosis patients to the ICU for management is costly without adding any additional benefit. However, this study was very small and may not have had adequate power to address a

difference between the study groups. It is also notable that individuals enrolled in the study had few comorbid medical conditions and were not critically ill. Further studies would be necessary to completely define the appropriate subgroup for treatment with subcutaneous insulin lispro.

Applications for Clinical Practice

In a highly selected group of individuals with uncomplicated diabetic ketoacidosis, treatment with subcutaneous lispro appears to be safe and produce similar outcomes when compared with standard therapies. In hospitals that require ICU admission for all patients receiving IV regular insulin infusions, insulin lispro is probably more cost-effective. However, more data are necessary to determine the ideal subset of patients who could benefit from this treatment strategy.

—Review by Harvey J. Murff, MD, MPH

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