

## **Insulin Analogs versus Human Insulin in the Treatment of Patients with Diabetic Ketoacidosis: a randomized controlled trial**

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*Objective:* To compare the safety and efficacy of insulin analogs and human insulins both during the acute intravenous (IV) treatment and during the transition to subcutaneous (SC) insulin in patients with diabetic ketoacidosis (DKA).

*Material and Methods:* In a controlled multi-center and open label trial we randomized patients with DKA to receive IV treatment with regular or glulisine insulin until resolution of DKA. After resolution of ketoacidosis, patients treated with IV regular insulin were transitioned to SC NPH and regular twice daily (n=34). Patients treated with IV glulisine insulin were transitioned to SC glargine once daily and glulisine before meals (n= 34).

*Results:* There were no differences in the mean duration of treatment or in the amount of insulin infusion until resolution of DKA between IV treatment with regular and glulisine insulin. After transition to SC insulin, there were no differences in mean daily BG levels, but patients treated with NPH/regular had higher rate of hypoglycemia (BG < 70 mg/dL). Fourteen patients (41%) treated with NPH/regular had 26 episodes of hypoglycemia and 5 patients (15%) in the glargine/glulisine had 8 episodes of hypoglycemia (p=0.03).

*Conclusions:* Regular and glulisine insulin are equally effective during the acute treatment of DKA. Transition to SC glargine and glulisine following resolution of DKA resulted in similar glycemic control but in a lower rate of hypoglycemia than NPH and regular insulin. Thus, a basal bolus regimen with glargine and glulisine is safer and should be preferred over NPH and regular insulin following the resolution of DKA.

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Diabetic ketoacidosis (DKA) is the most serious hyperglycemic emergency in patients with type 1 and type 2 diabetes mellitus. DKA is the most common cause of death in children and adolescents with type 1 diabetes and accounts for half of all deaths in diabetic patients < 24 years of age.(1) Recent series in adult patients with DKA have reported a mortality rate of less than 5%.(2; 3) DKA is responsible for > 100,000 hospital admissions in the United States and substantial costs related to direct and indirect costs.(2) It has been estimated that treatment of DKA episodes represent more than one of every four health care dollars spent on direct medical care for adult patients with type 1 diabetes.(4)

The mainstay in the treatment of DKA involves the administration of regular insulin via continuous IV infusion or by frequent subcutaneous (SC) or intramuscular (IM) injections of regular insulin or rapid-acting insulin analogs.(5-7) Although several controlled studies have shown that low-dose insulin therapy is effective regardless of the route of administration, most patients are treated with IV regular insulin until resolution of DKA.(8) When this occurs, SC insulin therapy can be started. The American Diabetes Association (ADA) recommends the transition to neutral protamine Hagedorn (NPH) and regular insulin twice daily or to a multi-dose regimen of short- or rapid-acting and intermediate- or long-acting insulins.(2; 8) Several studies have reported hospital rates of hypoglycemic events up to 37% with the use of NPH and regular insulin after discontinuation of IV insulin.(3; 9) The inadequate duration of action of NPH insulin and an undesirable peak activity at 4 – 6 h after injection(10) as well as the high day-to-day variability in absorption(11) partially explain the high rate of hypoglycemic events. In recent years, the use of long-acting basal and rapid-acting insulin analogs have been recommended as a more physiologic approach

than NPH and regular insulin for glucose control in the hospital;(12; 13) however, no previous studies have evaluated the safety and efficacy of insulin analogs in the management of patients with hyperglycemic crises. Accordingly, the aim of this multicenter, randomized, open label study was to i) determine differences in treatment response between regular insulin and rapid-acting insulin analogs during the acute IV treatment of DKA, and ii) determine differences between treatment with glargine plus glulisine and a split-mixed regimen of NPH plus regular after the transition to SC insulin following resolution of DKA.

## **MATERIAL AND METHODS**

A total of 74 patients with DKA were randomized in this study. Of them, 6 patients were excluded because 4 withdrew consent prior to or shortly after initiation of insulin therapy; 1 received glargine insulin prior to resolution of DKA, and 1 patient was treated with IV aspart insulin instead of regular insulin. The remaining 68 patients served as the study population. The diagnosis of DKA was established by standard criteria.(8) We excluded patients with systolic blood pressure less than 90 mm Hg after the administration of 1 liter of normal saline, comatose state, and patients with acute myocardial ischemia, congestive heart failure, end-stage renal or hepatic failure, dementia and pregnancy. This study was conducted at Grady Memorial Hospital, Atlanta, GA and at Hennepin County Medical Center, Minneapolis, MN, and was approved by dual institutional review boards.

Patients with DKA were randomly assigned in the Emergency Department to receive treatment with regular (n=34) or glulisine (n=34) insulin intravenously until resolution of DKA. After resolution of ketoacidosis, patients treated with IV regular insulin were transitioned to receive SC NPH and regular twice daily. Patients treated with

IV glulisine insulin were transitioned to glargine once daily and glulisine before meals.

**Treatment Protocols:** Patients were managed by members of the internal medicine residency programs of the respective institutions who received copies of the assigned treatment protocol (see Table A in the online appendix available at <http://care.diabetesjournals.org>). Orders for IV fluids, potassium and bicarbonate administration were similar in both groups and followed current ADA guidelines.(2; 8) Initial orders for IV regular and glulisine insulin included an initial bolus of 0.1 U/kg, followed by a continuous IV insulin calculated to deliver 0.1 U/kg/hour until BG levels decreased < 250 mg/dL (13.8 mmol/L). At that time, IV fluids were changed to dextrose containing solutions, and the insulin infusion rate was decreased to 0.05 U/kg/hour to maintain BG ~200 mg/dL (11.1 mmol/L) until resolution of DKA. DKA was considered resolved when BG was < 250 mg/dL, serum bicarbonate level was  $\geq$  18 mmol/L and venous pH was > 7.30.(2)

After resolution of DKA, insulin infusion was discontinued 2 hours after the administration of SC insulin. Patients with newly diagnosed diabetes received an initial total daily dose (TDD) of insulin of 0.6 U/kg/day. Subjects receiving insulin therapy prior to admission received the same outpatient insulin amount, with the TDD switched to glargine and glulisine or to NPH and regular on a unit-for-unit basis.

Patients treated with SC glargine and glulisine received 50% of TDD as glargine and 50% as glulisine insulin. Glargine was given once daily at the same time of the day and glulisine was given in three equally divided doses before each meal. Glargine was given at full dose independently of food intake, but to prevent hypoglycemia, the dose of glulisine was held if a subject was not able to eat a given meal. Patients treated with

NPH and regular received 2/3 of TDD before breakfast and 1/3 of TDD before dinner. The insulin dose was given as 2/3 NPH and 1/3 regular in the morning with breakfast, and 2/3 NPH and 1/3 regular in the evening with dinner. To prevent hypoglycemia, regular insulin was held if a subject was not able to eat a given meal; in addition, the dose of NPH was reduced by 50% in if a patient was kept NPO all day. Insulin dosage was adjusted daily according to glucose values to maintain a target BG < 140 mg/dL before meals. Insulin dose was adjusted and supplemental insulin was given based on BG levels (see Table B in the online appendix).

The primary outcome of the study was to determine differences in the rate of hypoglycemic events (BG < 70 mg/dl) during the transition period between treatment groups. Secondary outcomes include differences in the time to resolution of DKA and hyperglycemia, average BG during IV insulin infusion, mean daily BG after resolution of DKA, length of hospital stay, and hospital complications between treatment groups.

**Statistical analysis:** Based on previous reports, the rate of hypoglycemic events (primary endpoint) in patients treated with SC NPH and regular insulin was estimated to be 37%.(3; 9) The rate of hypoglycemic events with basal bolus insulin was estimated to be less than 10%.(14) Using two-sided chi-square test and type I error of 0.05, we calculated that 32 patients per group were needed to have 80% power to detect the difference in hypoglycemia rate of 30%. Allowing for 15% loss to follow-up, we recruited a total of 74 patients with DKA, of which 34 patients per group completed the study.

All data in the text, table and figures are expressed as mean  $\pm$  standard deviation. Two-sample Wilcoxon tests or Pearson's chi-squared tests were used to compare patient demographic and clinical characteristics as

well as outcomes measures between treatment groups. Cross-sectional analyses based on two-sample Wilcoxon tests were used to assess the group differences in BG and acid-based parameters during DKA treatment and mean daily BG after DKA resolution. We further employed repeated measures linear models to examine the group differences while adjusting for subject's age, gender, race and BMI. A p-value of <0.05 was considered significant. Statistical analysis was performed using SAS.

## RESULTS

The clinical characteristics of study patients on admission are shown in table 1. The mean age, duration of diabetes and precipitating cause for DKA were similar between treatment groups. Poor adherence with insulin therapy was the most common precipitating cause of DKA and was recorded in 59% of patients treated with glulisine and in 79% of patients in the regular insulin group. The length of hospital stay was similar between patients treated with glargine and glulisine ( $2.9 \pm 2.2$  days) and NPH and regular insulin ( $3.3 \pm 2.2$  days),  $P = NS$ .

Biochemical parameters on admission and during treatment were similar in patients treated with IV glulisine and regular insulin,  $P = NS$ . Changes in BG and acid-base parameters during treatment are shown in Figure 1. Suggested by the repeated measures analyses, the rate of decline of BG concentration and changes in acid base parameters during treatment were not significantly different between treatment groups while adjusting for age, gender, race, and BMI,  $P = NS$ . The mean duration of treatment until resolution of ketoacidosis was not statistically different between those treated with glulisine ( $8.9 \pm 4.7$  hour) and regular insulin ( $10.5 \pm 6.3$  hour),  $p = NS$ . At resolution of DKA, the mean BG concentration and acid-base parameters in patients treated with glulisine insulin

(glucose:  $153 \pm 61$  mg/dL, bicarbonate  $20 \pm 3$  mmol/L, pH:  $7.33 \pm 0.04$ , and anion gap:  $8.3 \pm 2.1$  mEq/L) were similar to those treated with IV regular insulin (glucose:  $185 \pm 58$  mg/dL, bicarbonate  $19.5 \pm 3.7$  mEq/L, pH:  $7.32 \pm 0.04$ , and anion gap:  $9 \pm 3$  mEq/L). During the insulin infusion, 6 patients in the glulisine and 4 patients treated with regular insulin developed one or two episodes of BG < 70 mg/dL, but none of them were less than 40 mg/dL. The amount of insulin administered until resolution of DKA ( $70 \pm 33$  units and  $76 \pm 46$  units) and the mean total duration of insulin infusion ( $15.7 \pm 4.5$  hours and  $20.5 \pm 12$  hours) were not different between glulisine and regular insulin, respectively,  $p = NS$ . There was no mortality and none of the patients had recurrence of DKA during their hospital stay.

After transition to SC insulin therapy, cross-sectional analyses based on two-sample Wilcoxon tests show that there are no significant differences in the mean daily glucose concentration between treatment groups. However, fitting repeated measures linear model with or without adjustment for age, gender, race, and BMI indicated a greater decline rate of BG in the glargine and glulisine group than that in the NPH and regular group ( $p < 0.01$ ).

Patients treated with NPH and regular insulin had a higher rate of hypoglycemic events than those treated with basal bolus regimen (Table 2). Fourteen patients (41%) treated with NPH and regular had 26 episodes of hypoglycemia and 5 patients (15%) in the glargine and glulisine group had 8 episodes of hypoglycemia ( $p < 0.01$ ). Three of these episodes in the NPH and regular and one in the glargine/glulisine group were less than 40 mg/dL. None of the episodes of hypoglycemia in either group were associated with loss of consciousness or seizure.

The total daily dose of SC insulin was similar between groups (Table 3). The mean total daily insulin dose including

supplemental was  $60 \pm 30$  units in the glargine and glulisine and  $58 \pm 24$  units in the NPH and regular group,  $p = \text{NS}$ . In addition, there were no differences in the amount of insulin supplements of insulin glulisine ( $13 \pm 10$  units) and regular insulin ( $12 \pm 6$  units) ( $p = \text{NS}$ ).

## **DISCUSSION**

This is the first prospective randomized trial that compared the use of insulin analogs and human insulins both during the acute IV treatment and during the transition to SC insulin in patients with DKA. During the initial treatment phase we observed no differences in the mean duration of treatment or in the amount of IV insulin administration until resolution of DKA between regular and glulisine insulin. After resolution of ketoacidosis, transition to SC glargine and glulisine insulin resulted in similar glycemic control compared to NPH and regular insulin; however, treatment with glargine and glulisine insulin is safer and is associated with significant lower rate of hypoglycemia. A total of 14 patients (41%) treated with NPH/regular and 5 patients (15%) in the glargine and glulisine had  $\geq 1$  episode of hypoglycemia ( $p < 0.03$ ).

The comparable response to IV glulisine and regular insulin during the acute resolution of DKA in this study is in line with previous reports of generally equal efficacy and in vivo potency of IV rapid-acting insulin analogs (glulisine, aspart, lispro) and regular insulin in animal and human studies.(15; 16) Pharmacokinetics and pharmacodynamic studies comparing the IV administration of glulisine and regular insulin have reported a similar onset of action within 20 minutes, a similar distribution and elimination profile, and equivalent glucose utilization and disposal on a molar, unit-per-unit basis.(16; 17) The present study confirms these observations and provides evidence on the equal efficacy and in vivo potency of IV

rapid-acting insulin analogs and regular insulin in patients with severe hyperglycemia and ketoacidosis. Their comparable in vivo potency is attributable to their similar receptor binding affinity and receptor-mediated clearance.(18) Our study and these previous reports indicate that treatment with IV glulisine and regular insulin are equally safe and efficacious in the acute management of patients with DKA. However, IV regular insulin is more cost effective and should be preferred over rapid-acting insulin analogues during the acute IV treatment phase of DKA.

Previous randomized studies in patients with DKA have focused on the amount and route of insulin administration during the acute resolution phase of ketoacidosis (2; 3). Few studies; however, have focused on the transition period to SC insulin after the resolution of DKA. Accordingly, this study aimed to compare differences between treatment with basal bolus insulin analogs and NPH and regular insulin after resolution of DKA. We found no differences in the daily glucose concentration between treatment groups; however, patients treated with NPH and regular insulin had higher rate of hypoglycemia (41%) compared to subjects treated with basal bolus (15%) insulin,  $p < 0.03$ . The rate of hypoglycemic event in this study is similar to the rate previously reported with the use of NPH and regular insulin after discontinuation of IV therapy.(3; 9)

The higher rate of hypoglycemia with human insulins is explained by the pharmacologic features and peak duration of action of NPH and regular insulin,(10) as well as the high day-to-day variability in absorption.(11) NPH has an onset of action ranging between 2 to 4 hours, a peak concentration of approximately 6 to 8 hours, and a duration of action up to 20 hours.(19) Regular human insulin has an onset of action in 30 minutes, peaks at 2 to 3 hours when given subcutaneously and has duration of

action of 6 to 8 hours.(19) The combination of basal and rapid-acting insulin analogs represents a more physiologic approach to glucose control in the hospital. Glargine is a peakless, long-acting basal insulin with an onset of action of approximately 2 hours, a plateau of biological action at 4 to 6 hours, and duration of action up to 24 hours.(20) Insulin glulisine has a faster onset of action and a shorter duration of action after SC injection compared with regular insulin.(21; 22) In agreement with these results, we recently reported that a basal bolus algorithm with glargine and glulisine is an effective intervention for glucose control with a low rate of hypoglycemic events (3%) in hospitalized patients with type 2 diabetes.(14) More recently, we reported that 38% of hospitalized patients treated with NPH and regular insulin combination experienced  $\geq 1$  episode of BG < 70 mg/dL during the hospital stay.(23) Minimizing the rate of hypoglycemia events is of major importance in hospitalized patients because it may represent an independent risk factor of poor clinical outcome.(24)

We acknowledge several limitations in our study including a relatively small number of patients and the fact that the large majority of patients were African Americans with poor adherence to therapy as the primary precipitating cause of DKA. We also excluded patients with hypovolemic shock, comatose state, acute myocardial ischemia, congestive heart failure, end-stage renal or hepatic failure, and pregnancy. A large

prospective, randomized clinical trial of strict glycemic control is certainly needed to address these important issues.

In summary, our study indicates that IV treatment with regular and glulisine insulin are equally effective with no differences in the mean duration of treatment or in the amount of insulin infusion until resolution of DKA. After resolution of DKA, transition to SC glargine once daily and glulisine before meals resulted in similar glycemic control but in a lower rate of hypoglycemic event than treatment with NPH and regular insulin twice daily. These findings indicate that a basal bolus insulin regimen with glargine and glulisine is safer and should be preferred over NPH and regular insulin following the resolution of DKA.

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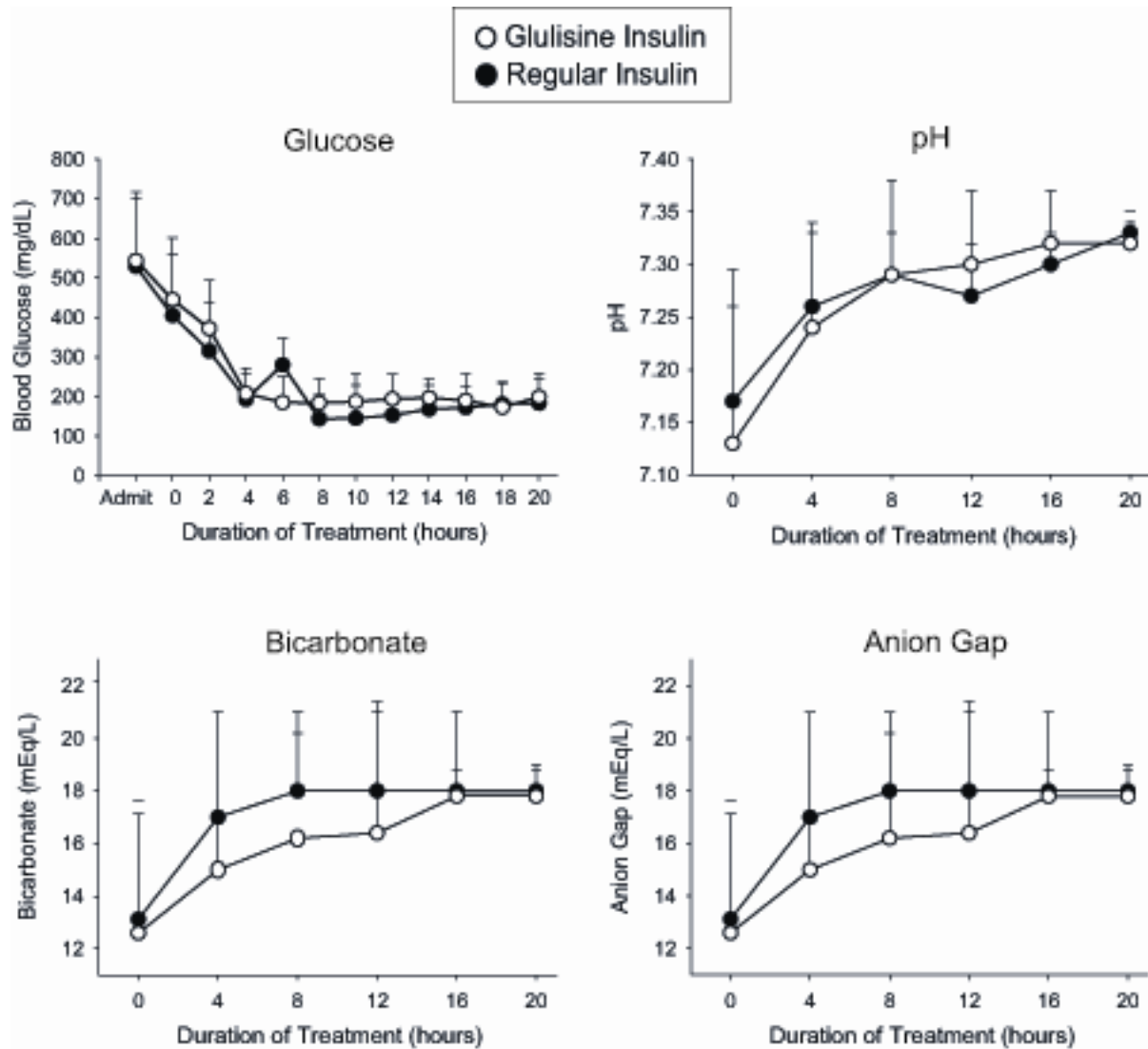
The sponsors of the study were not involved in the study design, data collection, analysis interpretation of the results, or preparation of the manuscript.

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**Figure 1.** Changes in metabolic profile in patients with DKA treated with intravenous glulisine (open circles) and regular insulin (close circles). To convert the values for glucose from mg/dL to millimoles per liter, multiply by 0.05551.



**Table 1.** Patient Characteristics on admission

	Insulin analogs (glulisine/glargine)	Human insulin (NPH/regular)
Number of patients	34	34
Age, year	39 ± 12	38 ± 12
Gender, M/F	22/12	23/11
Race		
African Americans	29	27
Caucasians	4	6
Other	1	
Body mass index, kg/m <sup>2</sup>	29 ± 9	27 ± 7
Precipitating cause of DKA		
Poor compliance, n (%)	20 (59)	27 (79)
New onset diabetes, n (%)	6 (18)	
Other medical illness, n (%)	8 (23)	7 (21)
Glucose, mg/dL	529 ± 173	564 ± 164
Bicarbonate, mEq/L	12.8 ± 4.5	12.5 ± 5.0
Venous pH	7.2 ± 0.1	7.1 ± 0.2
Anion gap, mEq/L	22 ± 6	22 ± 6
Beta-hydroxybutyrate, mmol/L	8.0 ± 3.4	7.4 ± 3.3
Hemoglobin A1C, %	11.7 ± 2.2	11.7 ± 2.9

Data are mean ± SD

**Table 2.** Hypoglycemic events during intravenous and subcutaneous insulin treatment

<b>Intravenous insulin therapy</b>		
	Glulisine	Regular
# patients with BG < 70 mg/dL, (%)	4 (12)	6 (18)
# episodes of BG < 70 mg/dL	6	7
# patients with BG < 40 mg/dL, n (%)	0 (0)	0 (0)
# episodes of BG < 40 mg/dL	0	0
<b>Subcutaneous insulin therapy</b>		
	Glargine/Glulisine	NPH/Regular
# patients with BG < 70 mg/dL, (%)		
# episodes of BG < 70 mg/dL	5 (15)	14 (41)*
# patients with BG < 40 mg/dL, n (%)	8	26**
# episodes of BG < 40 mg/dL	1 (3)	2 (6)
	1	2

BG: blood glucose

\*p= 0.03

\*\*p=0.019

**Table 3.** Mean blood glucose concentration and daily insulin doses during subcutaneous insulin treatment after resolution of DKA.

	Mean Daily Blood Glucose (mg/dL)			Mean Daily insulin dose (units/day)		
	NPH/Regular	Glargine/Glulisine	p value	NPH/Regular	Glargine/Glulisine	p value
Day 1*	188 ± 61	213 ± 76	0.234	50 ± 28	58 ± 33	0.304
Day 2	206 ± 71	220 ± 61	0.370	70 ± 37	73 ± 47	0.877
Day 3	207 ± 86	180 ± 80	0.417	77 ± 45	62 ± 49	0.364
Day 4	211 ± 63	158 ± 44	0.068	70 ± 47	67 ± 50	0.999
Day 5	190 ± 45	124 ± 41	0.068	50 ± 30	47 ± 41	0.302

\*Day 1= Depending on the time of resolution of ketoacidosis and transition to SC insulin, a patient could have received 1 or 2 doses of NPH/regular insulin or 1 dose of glargine and 1 to 3 doses of glulisine insulin per day.

Data are means ± SD.