Original Article

The Outcome of Using Long-Acting Insulin Glargine with Regular Insulin Infusion in Diabetic Ketoacidosis Patients with Renal Impairment: A Randomized Clinical Trial

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Abstract

Background: Diabetic ketoacidosis (DKA) is considered one of the most severe as well as immediate diabetes mellitus complications. A continuous infusion of regular insulin is the most effective technique for treatment. A long-acting insulin analog, including insulin glargine, is used to initially treat DKA by supplying background insulin. The study investigated the impact of insulin glargine on kidney disease patients with altered insulin pharmacokinetics and pharmacodynamics.

Materials and Methods: The current randomized controlled trial was conducted after obtaining institutional approval (R103/2020), with clinical trial registration (NCT05219942). Fifty-two subjects were randomized into two groups. The control group included patients who received a starting regular insulin infusion dose of 0.1 IU/Kg/hour and subcutaneous saline. The study group included patients who received regular insulin infusion and subcutaneous insulin glargine. The insulin glargine dosage was modified based on the glomerular filtration rate (GFR).

Results: The time required for DKA reversal was 21.15 ± 4.97 hr in controls and 17.00 ± 5.80 hr in the study group with p=0.008. The total insulin consumption until the reversal of DKA (units) in the control group was 130.85±10.31 while 108.00±21.52 in the study group and p<0.001. Rebound hyperglycemia 6 (23.1%) in controls and 1 (3.8 %) in the study group p=0.042. Intensive care unit (ICU) stay was 69.81±14.72 hr in the control group and 53.62±13.85 hr in the study group with p<0.001.

Conclusion: The addition of long-acting insulin glargine to intravenous regular insulin infusion reduces the time of DKA reversal and total insulin requirement with less liability of rebound hyperglycemia and could be safely used in renal impairment.

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Introduction

Despite being a preventable disease, diabetic ketoacidosis (DKA) is a relatively not uncommon presentation to the hospital. The biochemical triad of

acidaemia, hyperglycemia, and ketonemia is used to diagnose DKA (1).

Based on the current recommendations, a continuous infusion is the most efficient method for delivering regular insulin during DKA. The patients should be brought into the intensive care unit (ICU) for routine and meticulous monitoring. Electrolyte, acid-base, and dehydration imbalances are adjusted alongside insulin infusion, and co-morbid precipitating variables are recognized and addressed (2).

The Joint British Diabetes Societies' recommendation for the first treatment of DKA recommends maintaining a long-acting insulin analog, including insulin glargine, since it provides background insulin after intravenous (IV) insulin is terminated (3).

In addition to requiring less IV insulin overall and for a shorter time interval for DKA reversal, these patients also experienced much reduced post-intravenous insulin rebound hyperglycemia. Basal insulin was shown to be well tolerated and correlated with a speedier acidosis resolution with no negative effects (4, 5).

Healthy kidneys can filter >90 ml/min, and a decrease in GFR is associated with changes in glucose metabolism brought on by pharmacokinetic and pharmacodynamic changes in exogenously injected insulin, which is primarily removed by the kidney (6, 7).

The study investigated the effects of utilizing a long-acting insulin analog glargine during the resolution of DKA and the frequency of side events in patients with renal impairment whose insulin pharmacodynamics and pharmacokinetics have been altered.

Methods

The study was a randomized controlled trial at Ain Shams University, Egypt, intensive care unit, performed between January 2021 to July 2022. The institutional review board approved the study protocol with the number (R103/2020) and clinical trial registration (NCT05219942).

The Institutional Research Ethics Committee FMASU approved this study in a meeting held on 13/11/2020.

Ethical considerations

Protection of humans: no human tests were conducted for this research, also, all methods followed were in line with the requirements of the Declaration of Helsinki as well as the relevant clinical research ethics committee.

Confidentiality of data: the study adheres to the Declaration of Helsinki guidelines regarding publishing patient information.

Right to privacy and informed consent: The authors disclose that this publication contains no patient data. The patients or subjects presented in the paper have given their written permission after being fully informed. This document is held by the author to whom it corresponds.

The inclusion criteria were patients presenting with DKA aged 18–70 years old with Type I as well as Type II diabetes mellitus, both men and women. Patients receiving oral or injectable hypoglycemic medication. Diabetes has been present for over five years in both surgical and medical cases. Exclusion criteria were severe persistent hypotension (systolic blood pressure (SBP) 80 despite having normal saline (1000 ml)), end-stage renal disease or progressive renal failure, defined as eGFR 15 ml/min, acute myocardial infarction, pregnancy, and liver cell failure.

Study procedure: Fifty-two eligible patients were randomized into one of the two groups after patients or their legal guardians provided written informed consent. A computer-generated list derived from a database of random numbers was used to carry out the randomization. Staff (residents who gather data) were blinded to the specific therapy group to which a given participant was assigned; the researchers managed blinding and randomization.

The candidate cases were allocated into two groups of 26 patients, each at random after undergoing a history and physical examination, getting informed consent, and being admitted to the ICU. For the study group, during the first two hours after being admitted to the ICU, the patients received subcutaneous insulin glargine (Sanofi- Aventis LLC, Bridgewater, New Jersy, USA) and a starting regular insulin infusion of 0.1 IU/Kg/hour which changed according to the standard protocol of management (8). Insulin glargine dosage was changed to account for the calculated eGFR values (eGFR > 90 ml/ min dose = 0.27

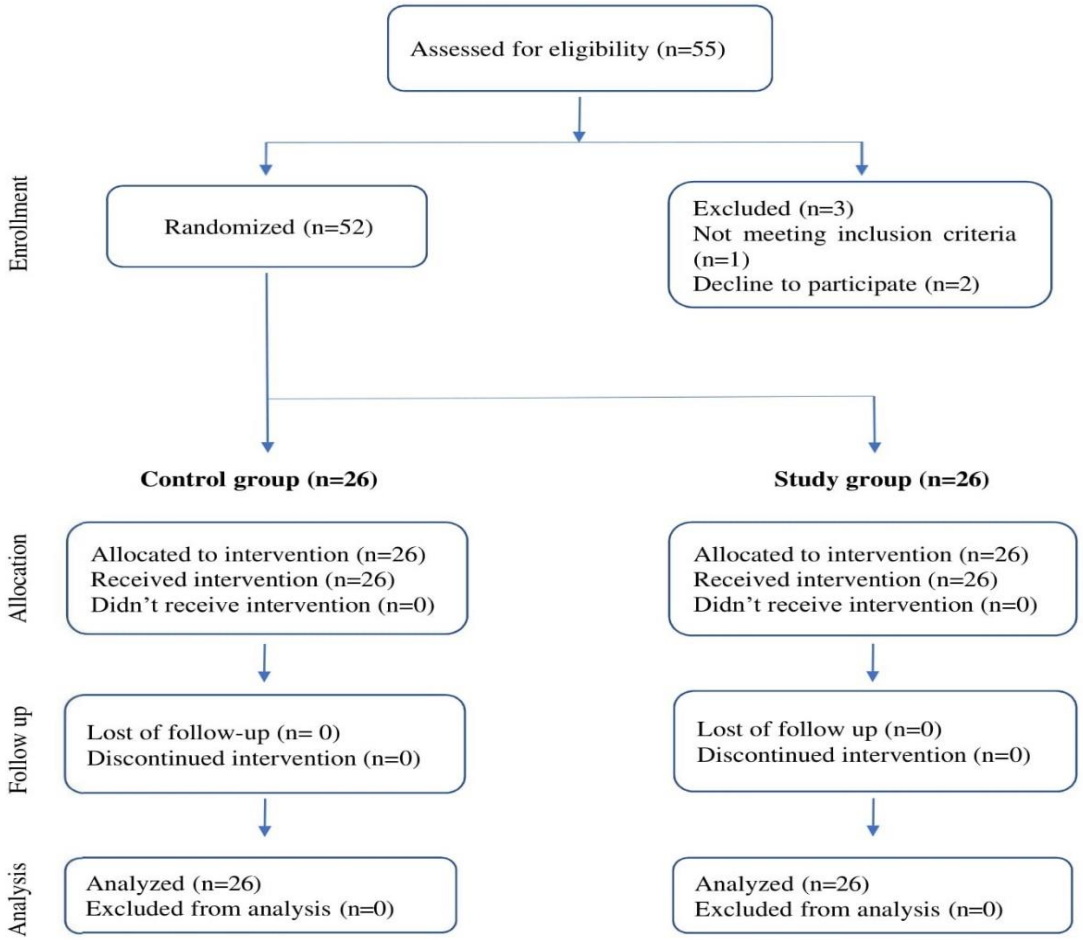

Figure (1): Flow consort chart

IU/kg/day, eGFR 60-89ml/min dose = 0.25 IU/kg/day, and eGFR 60 ml/min dose = 0.19 IU/kg/day) (9)**.** In the control group, subcutaneous saline was used in place of insulin glargine, while patients received a starting dose of 0.1 IU/Kg/hour regular insulin infusions. In both groups, when blood sugar levels began to drop below 250 mg/dl, the IV fluids were altered to half-normal saline (150-250 ml/hour) as well as dextrose at a concentration to maintain blood sugar in the 150-250 mg/dl range. Blood ketone level <0.6 mmol/L, bicarbonate >15.0 mmol/L, and a blood sugar level of 200 mg/dl, pH >7.3 units, were needed for the resolution of DKA. Subcutaneous insulin is switched to one to two hours before stopping insulin infusion (8)**.**

The study excluded patients who declined to continue the study protocol or died while it was still ongoing. The primary outcomes were the mean time to reverse DKA and total insulin consumption. The secondary outcomes included hypoglycemia, hypokalemia, rebound hyperglycemia frequency, as well as the length of ICU hospitalization.

Sample size: Using the Power Analysis and Sample Size (PASS 11 software, 2011, NCSS, LLC, Kaysville, Utah, USA). When the sample area under the curve (AUC) in the receiver operating characteristic analysis (ROC) is 0.5, a random sample of 26 instances (in each group) yields a two-sided 95 percent confidence interval (width of 0.3).

Statistical analysis: The data were coded using the 23rd version of IBM SPSS. In terms of the quantitative data, ranges, standard deviations, and means were

displayed. Additionally, quantitative data were represented by percentages and numbers. The Chi-square test was utilized for comparing groups using qualitative data. An independent t-test was utilized to compare two groups with a parametric distribution as well as numerical data. The survival rates of the two analyzed groups for DKA clearance and ICU stay were calculated using a Kaplan-Meyer analysis and a log-rank test. The confidence interval was established at 95 percent, whereas the acceptable margin of error was established at 5 percent. Therefore, the level of the p-significance value was determined at 0.05.

Results

Initially, 55 patients were enrolled in the present study. During the enrollment phase, three patients were excluded; two declined to participate, and the third did not fit our inclusion requirements. Fifty-two patients, 26 from each of the two groups, completed the trial successfully (Figure 1), with no substantial differences between the demographics of both groups (Table 1). Reversing DKA required 21.15 ± 4.97 hours in the control group but only 17.00 ± 5.80 hours in the study group. There were statistically substantial differences between both groups (p = 0.08). A total of 130.85 ± 10.31 units of regular insulin were administered to the control group until the DKA was reversed, as opposed to 108.00 ± 21.52 units in the study group (Table 2). Kaplan-Meier survival analysis was performed to compare the two groups' DKA reversal times (Figure 2). A pairwise log-rank test was performed to detect any differences in the distributions for the two groups, as depicted in (Table 3). There was no statistically significant difference between the two groups when comparing the occurrence of mortality, comorbidities, hypoglycemia, or hypokalemia (Table 2). Rebound hyperglycemia 6 (23.1%) in controls and 1 (3.8 %) in the studied cases p =0.042. ICU stays were statistically significantly shorter in the study group (53.62 ±13.85 hours) than in the control group (69.81 ±14.72 hours) (p =0.001). Kaplan-Meier survival analysis was conducted on the two groups to compare the length of interval each group stayed in the ICU (Figure 3). A pairwise log-rank test was performed to determine

Table 1: Comparison between the two groups regarding demographic data and characteristics

Variable		Control group (N = 26)	Study group (N = 26)	Test value	P-value
Age (yrs)	Mean±SD	30.0 ± 6.57	33.12 ± 7.83	-1.554•	0.127
	Range	18 – 45	20 – 47		
Sex	Females	12 (46.2%)	14 (53.8%)	0.308*	0.579
	Males	14 (53.8%)	12 (46.2%)		
Type of DM	I	17 (65.4%)	15 (57.7%)	0.325*	0.569
	II	9 (34.6%)	11 (42.3%)		
Duration of DM (yrs)	Mean±SD	15.35 ± 2.73	14.38 ± 3.90	1.030•	0.308
	Range	11 – 22	7 – 22		
Weight (kg)	Mean±SD	77.85 ± 14.53	82.54 ± 8.86	-1.406•	0.166
		56 - 100	68 - 105		
Predisposing factor	Medical	18 (69.2%)	21 (80.8%)	0.923*	0.337
	Surgical	8 (30.8%)	5 (19.2%)		

•: Independent t-test; *: Chi-square test. P>0.05: Non significant (NS); P <0.05: Significant (S); P <0.01: Highly significant (HS). N, number; SD, standard deviation.

Table 2: Comparison between both groups regarding laboratory data and outcomes

Variable		Control group (N = 26)	Study group (N = 26)	Test value	P-value
Total insulin dose (units)	Mean±SD	130.85 ± 10.31	108.00 ± 21.52	4.883*	<0.001
	Range	115 – 150	75 – 145		
DKA clearance (hr)	Mean±SD	21.15 ± 4.97	17.00 ± 5.80	2.774*	0.008
	Range	14 – 30	10 – 30		
Hypoglycemia	Negative	24 (92.3%)	25 (96.2%)	0.354*	0.552
	Positive	2 (7.7%)	1 (3.8%)		
Hypokalemia	Negative	25 (96.2%)	24 (92.3%)	0.354*	0.552
	Positive	1 (3.8%)	2 (7.7%)		
Rebound hyperglycemia	Negative	20 (76.9%)	25 (96.2%)	4.127*	0.042
	Positive	6 (23.1%)	1 (3.8%)		
Mortality	Negative	25 (96.2%)	24 (92.3%)	0.354*	0.552
	Positive	1 (3.8%)	2 (7.7%)		
ICU stay (hr)	Mean±SD	69.81 ± 14.72	53.62 ± 13.85	4.085*	<0.001
	Range	49 – 103	36 – 89		

•: Independent t-test; *: Chi-square test. P>0.05: Non significant (NS); P <0.05: Significant (S); P <0.01: Highly significant (HS). N, number; SD, standard deviation.

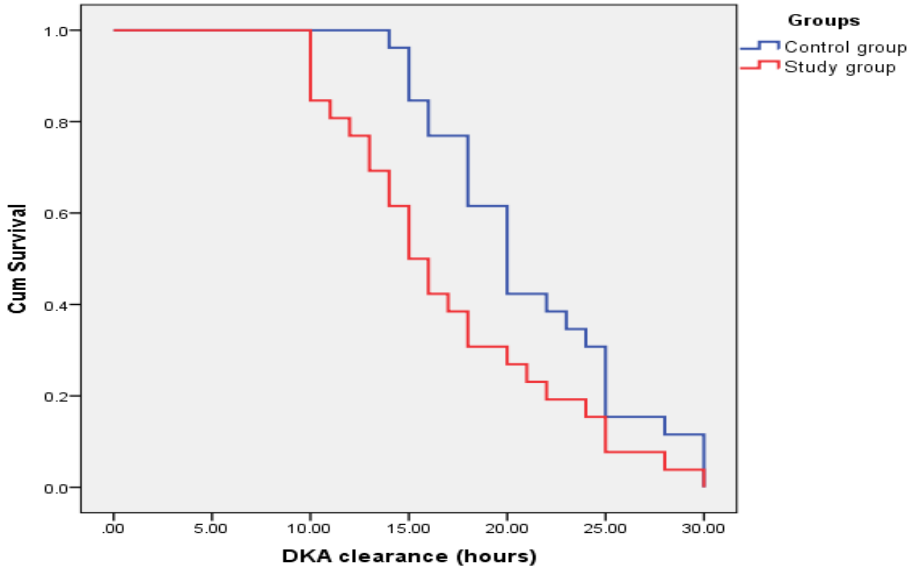

Figure 2. Kaplan-Meier survival plot representing the time for DKA clearance (hr) in the two groups.

distribution differences between both groups (Table 4).

Discussion

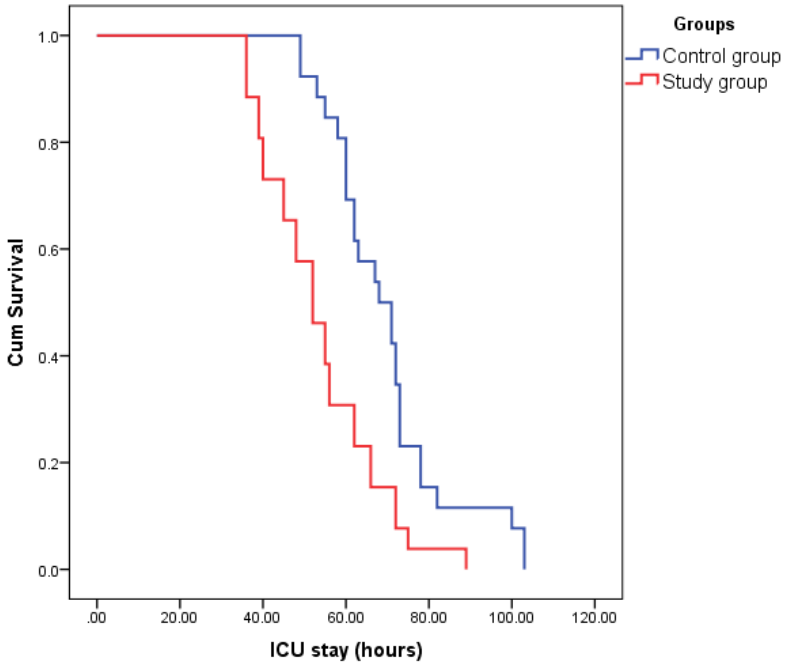

Figure 3. Kaplan-Meier survival plot representing the ICU stay in the two groups.

Table 3: Comparison between the two groups regarding time for DKA clearance (hr) by Kaplan Meyer analysis.

Groups	Mean	SE	95% CI		Median	SE	95% CI		Log Rank Test	
			Lower	Upper			Lower	Upper	X^2	P-value
Control group	21.15	0.98	19.24	23.06	20.00	1.01	18.03	21.98	5.179	0.023
Study group	17.00	1.14	14.77	19.23	15.00	1.02	13.00	17.00		

P>0.05: Non significant (NS); P <0.05: Significant (S).

The pharmacokinetic characteristics of long-acting insulin analogs are comparably flat. In the past, insulin glargine has successfully treated both type 1 as well as type 2 diabetes Mellitus (T1DM) and (T2DM) (10). In comparison to neutral protamine Hagedorn (NPH) insulin, it is as effective in controlling blood sugar levels (11)**,** less prone to cause hypoglycemia, and offers a consistent supply of basal insulin (12, 13)**.** Insulin dosage adjustments may be necessary as GFR decreases as a result of decreased renal clearance. In

Table 4: Comparison between the two groups regarding ICU stay (hr) by Kaplan Meyer analysis.

Groups	Mean	SE	95% CI		Median	SE	95% CI		Log Rank Test		
			Lower	Upper			Lower	Upper	X^2	P-value	Sig.
Control group	69.808	2.887	64.15	75.465	68	5.099	58.006	77.994	11.570	<0.001	HS
Study group	53.615	2.716	48.291	58.939	52	3.559	45.025	58.975			

P>0.05: Non significant (NS); P <0.05: Significant (S); P <0.01: Highly significant (HS).

addition to increasing the likelihood of hypoglycemia in patients with severe T2DM and renal failure, insulin glargine treatment improved glucose control safely and efficiently (14, 15).

One of the severe and immediate consequences of diabetes mellitus is DKA (16). In the present study, the calculated eGFR was used to adjust the insulin glargine dosage. The length of time until a DKA reversal and the total amount of insulin consumed before the reversal of DKA were statistically different between the two groups. In terms of the effects, the control group required a longer stay in the ICU and had greater rebound hyperglycemia.

To evaluate the efficiency as well as insulin glargine safety in patients with an eGFR of 60 and lower, Majumder and colleagues found that the risk of hypoglycemic episodes substantially decreased while HbA1c remained below tolerable limits. Given the paucity of information regarding the use of basal insulin in advanced CKD, insulin glargine may also be considered a safe and practical alternative (17).

Fewer studies have been published on the effects of long-lasting insulin analogs for treating DKA compared to short-acting insulin analogs. Shankar et al. found that adding insulin glargine to standard treatment significantly decreased the time it took for a child to recover from DKA and the amount of needed insulin. They compared 59 children who only received intravenous insulin with 12 children with DKA (moderate to severe) who were subjected to insulin glargine 6 hours following starting intravenous regular insulin. The usual group recovered from DKA in 17.1± 2.6 hours, whereas the intervention group did so in 12.4±2.9 hours (p=0.001) (18).

Using data from 380 DKA events in hospitalized patients, Mohamed et al reported a safe use of early insulin glargine with a trend toward faster DKA recovery (19). Hsia et al. researched 61 diabetic patients (25 DKA cases) to find out if providing subcutaneous insulin glargine as well as an intravenous infusion of regular insulin may prevent rebound hyperglycemia after quitting insulin. Up to 12 hours following the end of the insulin infusion, rebound hyperglycemia was detected in 33.3 percent of the studied group (who were subjected to intravenous regular insulin plus insulin glargine) and in 93.5% of controls (receiving intravenous insulin only) ($p<0.001$). They concluded that adding insulin glargine to intravenous insulin is a safe method that dramatically lowers the risk of rebound hyperglycemia and hypoglycemia (20). In the study by Houshyar and colleagues, adding insulin glargine reduced the typical recovery time from DKA without causing any bouts of hypoglycemia or hypokalemia. Furthermore, the quantity of insulin needed, hospitalization interval, and duration necessary to recover from DKA were shortened (21).

Our study had limitations, including the relatively small sample size, while larger studies will be needed to confirm these findings. The study covered patients with any severity of DKA (mild, moderate, and severe).

Conclusion

The addition of long-acting insulin glargine to standard infusion of regular insulin had a beneficial effect in reducing the time of reversal DKA and total insulin requirement with less liability of rebound hyperglycemia and could be safely used in renal impairment.

Acknowledgment

None.

Conflicts of Interest

The authors declare that they have no conflict of interest.

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