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# ENHANCING RECOVERY IN DIABETIC KETOACIDOSIS: THE ROLE OF BASAL INSULIN (GLARGINE) WITH INTRAVENOUS INSULIN INFUSION

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## ABSTRACT

**Background:** One of the most life threatening metabolic complication of diabetes mellitus (DM) and with a high mortality rate is diabetic ketoacidosis (DKA).

**Objectives:** To evaluate the use of insulin glargine in addition to intravenous insulin infusion in treatment of DKA.

**Methods:** This multi-centered prospective cross sectional analytical study was carried out at Department of Emergency of all three different campuses of Ziauddin University, Karachi for six months (January 2023 to June 2023) using non-probability consecutive sampling. The International Society for Pediatric and Adolescent Diabetes (ISPAD) Clinical Practice Consensus Guidelines 2018 were used for diagnosing DKA. Through simple random technique, patients were divided into group A (Insulin infusion only) and group B (Insulin + Insulin Glargine infusion). SPSS version 23.0 was used for analyzing data. Independent t-test was applied for the laboratory findings which were compared between group A and group B.

**Results:** A total of 139 DKA patients (mean age 54.6 years, 61.9% female) were studied. At baseline, they presented with severe hyperglycemia, acidosis, and elevated anion gap. After 6 hours, both groups showed significant glucose reduction, with no difference between insulin infusion alone and insulin plus glargine. However, patients receiving glargine demonstrated faster metabolic recovery, reflected by higher bicarbonate, improved arterial pH, and lower anion gap. Renal function and osmolality improved similarly in both groups.

**Conclusion:** Adding basal insulin (glargine) to standard intravenous insulin infusion accelerated the resolution of metabolic acidosis and improved biochemical recovery in DKA patients, without affecting glucose reduction or renal function.

**Keywords:** Diabetic Ketoacidosis, Insulin Glargine, Metabolic acidosis, Regular Insulin

## INTRODUCTION

One of the most life-threatening metabolic complication of diabetes mellitus (DM) and with a high mortality rate is diabetic ketoacidosis (DKA) [1]. However despite of DKA being a preventable

disease, it is not an uncommon presentation to the Emergency Room (ER) of the hospital [2]. For diagnosing DKA, a triad of three biochemical changes viz. hyperglycemia, acidemia and ketonemia are used. The pre-existing ranges of mortality rate vary from 17 % to 50 % [3].

On the basis of the existing and latest recommendations, continuous infusion is currently considered one of the most effective methods for regular insulin delivery to tissues of DKA patients [4]. For effective and meticulous monitoring of DKA patients, they must be shifted to intensive care unit (ICU) for continuous surveillance [5]. Imbalances of dehydration, acid-base and electrolytes are necessary to be adjusted alongside infusion of insulin in addition to precipitation of co-morbid variables that also need to be addressed [6].

The recommended first line DKA treatment by the Joint British Diabetes Society is an analog of long-acting insulin such as insulin glargine as it aids in provision of background insulin post-intravenous insulin (IV) termination [7]. Additionally, this leads to lesser IV insulin overall as well as short interval of time for reversal of DKA [8]. Such patients might also experience a decrease in rebound hyperglycemia followed by intravenous insulin [9].

Use of glargine, an analogue of insulin has remained a drug of special interest since it is considered as the first line of insulin choice among diabetics [10]. It has longer half-life when used through sub-cutaneous (SC) route [11]. It has demonstrated effects comparable to regular insulin when intravenously injected or administered intra-muscularly (IM) [12]. Published data has shown that basal insulin (glargine) when started right after diagnosis of DKA is established showed better patient recovery [13]. Studies have reported patient survival rate of nearly 100 % with shorter duration of hospital stay with the use of bolus-treatment, regarded as feasible alternative to the traditional treatments [14]. Various researchers have shown that ketoacidotic diabetic patients have observed that using IM or SC route are safer as well as effective for treating DKA [15].

A synergistic effect is observed with the use of insulin glargine alongside intravenous insulin in recovery from DKA. However, published literature is scarce in this regard and even more so limited in terms of local literature. As reported in a study from Karachi, Pakistan, the estimated existing prevalence of Diabetes Mellitus associated DKA in patients have been reported around 10 % [16]. International literature has stated the incidence of hyperglycemic emergencies with a mortality ranging from 04 to 40 % in population residing in developed countries such as the US [17]. The objective of this study was to evaluate the use of insulin glargine in addition to intravenous insulin infusion in treatment of DKA.

## METHODS

This multi-centered prospective cross sectional analytical study was carried out at the Department of Emergency of all three different campuses of Ziauddin University, Karachi. [Ethical Approval Reference Code-5570622MWEM] The campuses included the ones in Clifton, Kemari and North areas of Karachi. The duration of study was six months (from January 2023 to June 2023). Using non-probability consecutive sampling, patients between 18 to 70 years, presenting to the emergency room of the hospital, diagnosed with DKA either having type I or type II diabetes mellitus were included in the study. Patients on oral or injectable hypoglycemic drugs, and having diabetes mellitus (minimum 5 years) were included. In terms of exclusion criterion, patients with severe persistent hypotension (a systolic blood pressure of <80 mmHg despite given 1000 ml normal saline via parenteral route, with any known cardiovascular disease, pregnant females and with liver dysfunction were excluded from the research.

The sample size for the study was calculated keeping the following variables given below. The sample size came out to be 139 at 5 % margin of error and 95 % confidence level [16].

**Sample Size for Frequency in a Population**

| | |
|---|---|
| Population size(for finite population correction factor or fpc)(*N*): | 1000000 |
| Hypothesized % frequency of outcome factor in the population (*p*): | 10%+/-5 |
| Confidence limits as % of 100(absolute +/- %)(*d*): | 5% |
| Design effect (for cluster surveys-*DEFF*): | 1 |

**Sample Size($n$) for Various Confidence Levels**

| Confidence Level(%) | Sample Size |
|---|---|
| 95% | 139 |
| 80% | 60 |
| 90% | 98 |
| 97% | 170 |
| 99% | 239 |
| 99.9% | 390 |
| 99.99% | 545 |

Equation

Sample size $n = [DEFF*Np(1-p)]/ [(d^2/Z^2_{1-\alpha/2}*(N-1)+p*(1-p)]$

Results from OpenEpi, Version 3, open source calculator—SSPropor

The diagnosis and management of DKA was carried out in line with the International Society for Pediatric and Adolescent Diabetes (ISPAD) Clinical Practice Consensus Guidelines 2018 [17]. In accordance with the guidelines, DKA was diagnosed via symptoms and laboratory testing triad viz. hyperglycemia, acidemia and ketosis. A known diabetic with blood glucoses levels >11.0 mmol/L, bicarbonate (HCO3) <15.0 mmol/L and / or blood pH <7.3 and ketonemia- >3.0 mmol/L or with significant ketonuria (>2+ on standard urine stick test) and anion gap of 15 mmol/L.

Clinical presentation of patients, precipitating factors and response to treatment to infusion of intravenous insulin only (group A) and to infusion of basal insulin (glargine) alongside intravenous insulin infusion were compared. Through simple random technique, patients were divided into group A and B. All the details of patients were recorded on a self-designed questionnaire. Blood samples were taken at time of admission and sent for bicarbonate and ketone body level estimation. Using glucometer, blood glucose levels were recorded. Informed consent was sought from all patients prior to inclusion in the study. If any patient refused participation at any point of data collection, their data was removed from the study. SPSS version 23.0 was used for analyzing the data. For categorical variables, frequency and percentages were reported. For continuous variables, normality of data was tested using Shapiro-Wilk test (p-0.2) which came back insignificant, therefore the data was presented as mean and standard deviation. Independent t-test was applied for the laboratory findings which were compared between group A and group B.

## RESULTS

Table 1 presents the baseline demographics of 139 patients included in the study. The mean age of participants was 54.55 ± 12.78 years, with a mean BMI of 22.82 ± 3.65 kg/m². The majority of patients were female 86 (61.9 %), while males accounted for 53 (38.1 %). All patients were known diabetics, and 27 (19.4 %) had a prior history of DKA. Regarding diabetes management, 66 (47.5 %) were on oral hypoglycemic drugs, 60 (43.2 %) were on injectable insulin, and 13 (9.4 %) were not on any treatment at the time of presentation.

**Table 1- Baseline demographics of DKA patients included in the study (n=139)**

| Variables | | Values Frequency (%) / Mean ± SD |
|---|---|---|
| **Mean Age (years)** | | 54.55 ± 12.78 |
| **Mean BMI (kg/m$^2$)** | | 22.82 ± 3.65 |
| **Gender** | **Male** | 53 (38.1 %) |
| | **Female** | 86 (61.9 %) |
| **Known Diabetic** | | 139 (100 %) |
| **History of DKA** | | 27 (19.4 %) |
| **On Diabetes Treatment** | **Oral Hypoglycemic drug/s** | 66 (47.5 %) |
| | **On Injectable Insulin** | 60 (43.2 %) |
| | **None** | 13 (9.4 %) |

Table 2 summarizes the laboratory findings at baseline prior to initiation of treatment. Patients presented with severe hyperglycemia, with mean blood glucose of 19.57 ± 12.55 mmol/L (range 12.85–34.12). The mean bicarbonate level was 12.88 ± 3.4 mmol/L, reflecting significant metabolic acidosis; with a mean arterial pH of 6.95 ± 0.85 (range 6.7–7.2). The mean anion gap was 19.75 ± 1.7 mmol/L. Renal function was impaired, with a mean creatinine of 177 ± 62 µmol/L (range 52–345). Serum osmolality at presentation averaged 295 ± 35 mOsm/kg(range 266–335).

**Table 2- Laboratory findings of included patients prior to start of treatment (n=139)**

| Variables | Mean ± SD (range) |
|---|---|
| **Glucose (mmol/L)** | 19.57 ± 12.55 (12.85-34.12) |
| **Bicarbonate (mmol/L** | 12.88 ± 3.4 (5.8-13.5) |
| **Creatinine (umol/L)** | 177 ± 62 (52-345) |
| **Osmolality (mosm/kg)** | 295 ± 35 (266-335) |
| **Arterial pH** | 6.95 ± 0.85 (6.7-7.2) |
| **Anion gap (mmol/L)** | 19.75 ± 1.7 |

Table 3 shows the comparison of treatment outcomes between patients managed with insulin infusion only (Group A, n=69) and those treated with insulin infusion plus basal insulin glargine (Group B, n=70) after 6 hours of therapy. Mean blood glucose decreased comparably in both groups (11.2 ± 1.88 mmol/L in Group A vs. 10.95 ± 2.1 mmol/L in Group B, p-0.18). However, significant improvements were observed in metabolic recovery markers among Group B patients. Bicarbonate levels were significantly higher (21.5 ± 1.9 vs. 17 ± 2.5 mmol/L, p-0.006), arterial pH was better corrected (7.28 ± 0.09 vs. 7.17 ± 0.13, p-0.001), and the anion gap was narrower (15.5 ± 2.9 vs. 16.8 ± 3.26 mmol/L, p=0.007) compared to Group A. No significant differences were found between groups regarding creatinine (p-0.3) or osmolality (p-0.10). The time required for reversal of DKA in group A was 18.52 ± 4.75 hours while in group B was 15.28 ± 5.1 (p-0.001).

**Table 3- Comparison of treatment outcomes between group A (Insulin infusion only) and group B (Insulin + Glargine infusion)- 12 hours after treatment (n=139)**

| Variables | Group A Insulin Infusion Only(n= 69) | Group B Insulin + Glargine Infusion (n=70) | P-value |
|---|---|---|---|
| **Glucose (mmol/L)** | 11.2 ± 1.88 | 10.95 ± 2.1 | 0.18 |
| **Bicarbonate (mmol/L** | 17 ± 2.5 | 21.5 ± 1.9 | **0.006*** |
| **Creatinine (umol/L)** | 98 ± 20.26 | 95 ± 19.78 | 0.3 |
| **Osmolality (mosm/kg)** | 445 ± 55 | 478 ± 61 | 0.10 |
| **Arterial pH** | 7.17 ± 0.13 | 7.28 ± 0.09 | **0.001*** |
| **Anion gap (mmol/L)** | 16.8 ± 3.26 | 15.5 ± 2.9 | **0.007*** |
| **Time required for DKA reversal (hrs)** | 18.52 ± 4.75 | 15.28 ± 5.1 | **0.001*** |

## DISCUSSION

A total of 139 patients with diabetic ketoacidosis (DKA) were included, with a mean age of 54.6 years and a female predominance (61.9%). All patients were known diabetics, and about one-fifth had a prior history of DKA. Nearly half were on oral hypoglycemic drugs, while 43% were on insulin therapy at presentation. At baseline, patients demonstrated severe metabolic derangements,

including marked hyperglycemia (mean glucose 19.6 mmol/L), low bicarbonate (12.9 mmol/L), metabolic acidosis (mean pH 6.95), elevated anion gap (19.8 mmol/L), and impaired renal function (mean creatinine 177 μmol/L). After 6 hours of treatment, both groups showed improvement in glycemic and metabolic parameters. Blood glucose reduction was comparable between the insulin infusion only group (Group A) and the insulin plus glargine group (Group B). However, Group B demonstrated significantly greater metabolic recovery, with higher bicarbonate levels, better correction of arterial pH, and a lower anion gap. Renal function and osmolality improved in both groups without significant differences.

The published literature also reports similar findings to our study. In terms of demographics, a local study reported female predominance of DKA in 58 % of patients while in our study, 62 % of patients with DKA were females [16]. History of DKA was reported in 27 (19.4 %) of patients in our research. Likewise, in another study, 27 % of patients were reported to have previous history of DKA [18].

In our study, a significant difference of bicarbonate levels, arterial pH and anion gap was observed between insulin infusion only and insulin + glargine infusion group. All three levels were found to be better in group B as compared to group A. Even though both treatments were able to near-to-normalize various parameters, group B was better able to bring the parameters near-to-normal. Similar findings have been observed in studies from Afro-Caribbean, Japanese and even the South Asian populations [19-21].

In line with our study, Ammar et al in a randomized controlled trial in DKA patients divided into groups (like in our study), concluded that addition of long acting insulin glargine to intravenous infusion of regular insulin reduced the time taken for reversing DKA with less chances of rebound hyperglycemia and was safely used even in patients with renal impairment [22]. Similar observations were reported by Majumder et al in their research as well [23].

A major strength of this study is its multi-centered design, which enhances the generalizability of the findings across different patient populations and clinical practices. With a sample size of 139 patients, the study had sufficient power to detect meaningful differences in metabolic recovery between treatment groups. The use of standardized biochemical assessments at six hours allowed robust comparison of early treatment effects, while reliance on objective laboratory measures such as pH, bicarbonate, and anion gap minimized the potential for bias. Furthermore, this study is one of the few in the region to evaluate the role of early basal insulin in combination with intravenous infusion for diabetic ketoacidosis, thereby contributing novel evidence to local clinical practice.

Despite these strengths, the study has some limitations. The relatively short follow-up period of six hours provided insights into early biochemical improvements but did not assess complete DKA resolution, recurrence, or longer-term outcomes. The absence of randomization or blinding may have introduced treatment allocation bias, while variability in supportive care practices such as fluid and electrolyte management across centers could have influenced the results despite standardized protocols. Additionally, the study did not evaluate important clinical endpoints such as hypoglycemia, length of ICU or hospital stay, or mortality, which would have provided a more comprehensive picture of the intervention's impact. Finally, assessing outcomes at only a single time point limited the ability to evaluate the trajectory of recovery over time.

Based on these findings, further research is recommended in the form of randomized controlled trials with larger and more diverse populations to confirm and expand upon the observed benefits of adding glargine to intravenous insulin infusion. Future studies should include longer follow-up to assess the time to complete DKA resolution, length of hospital stay, insulin requirements, and potential adverse events. Incorporating cost-effectiveness analyses would also help determine the economic feasibility of routine early glargine use in resource-constrained settings. Moreover, evaluating long-term outcomes such as recurrent DKA episodes, post-discharge glycemic stability, and treatment adherence could strengthen the evidence base for integrating basal insulin into standard DKA management protocols. Ultimately, these efforts may guide the development of clinical practice guidelines that optimize care and improve recovery for patients with diabetic ketoacidosis.

## CONCLUSION

Adding basal insulin (glargine) to standard intravenous insulin infusion accelerated the resolution of metabolic acidosis and improved biochemical recovery in DKA patients, without affecting glucose reduction or renal function.

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