Research Protocol

Title: Early basal insulin administration in adult diabetic ketoacidosis management

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NCT Number: 04567225

Document Date: 07/22/2021

Research Protocol Template
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I. BACKGROUND AND SIGNIFICANCE

Diabetic ketoacidosis (DKA) is a potentially life-threatening metabolic complication in adults with type 1 diabetes (1). Intravenous Insulin Infusion (IVII) is the management cornerstone. This will later transition to subcutaneous (SC) basal Insulin with DKA resolution, signaled by anion gap (AG) closure. Transition usually happens after AG closure and two hours before IVII discontinuation (2). However, the transition is often followed by a rebound hyperglycemia, particularly if there are high insulin requirements that can adversely affect the DKA recovery, increase LOS, morbidity, and mortality (3).

Early administration of basal insulin has seldom been studied in DKA management. In 2012, Hsia et al (4) conducted a prospective randomized controlled trial involving 61 hospitalized adults with known diabetes and presented by hyperglycemia who were randomized to receive treatment with IV insulin infusion (IVII) with or without glargine (0.25 Unit/kg). The primary outcome of rebound hyperglycemia was reduced with early administration of glargine (33.3% vs 93.5%, $P < 0.001$) without increasing the risk of hypoglycemia (none in the intervention group vs three cases in the control group). Accordingly, in 2013, the Joint British Diabetes Societies updated their guideline on DKA management in adults to advise early administration of home basal insulin dose (5). After that, two randomized controlled trials were published in 2015, both with a sample size of 40 patients, investigated initiating Insulin Glargine within 2-3 hrs from IVII initiation compared to IVII alone, using a dose of 0.3 unit/kg (6) and 0.4 unit/kg (7). Although both the studies did not demonstrate statistical significance in the primary and secondary outcomes, it could be argued they were clinically significant. For examples, time to AG closure 13 +/- 6 vs 16 +/- 6 hours, IVII dosage 84 ±45 U vs 116 ± 91 U, rebound hyperglycemia for 24 hours after DKA resolution 35% vs 51%, hospital LOS 5.1 vs 5.9 days (intervention and control groups respectively) (7) and no difference in hypoglycemia events between both groups in both studies.

The limitations in the previous studies such as being underpowered, flaws in reporting data, and lacking a unified management protocol make it difficult to state a definitive evidence-based recommendation for using basal insulin early in DKA in adults. For that reason, we propose prospective, open-label, intervention cohort study to test our hypothesis that an insulin glargine dose of 0.4 Units/kg early administered (within four hours) of IVII initiation in DKA management in adult would be effective and safe in shortening the time to anion gap closure comparing to the standard practice.

II. STUDY OBJECTIVE(S): INCLUDING SPECIFIC AIMS AND/OR HYPOTHESES

Specific Aim 1: Test the hypothesis that early Glargine 0.4 unit/kg administration within 4 hours from IV insulin initiation will provide faster anion gap closure in Diabetic Ketoacidosis management in MICU, at least 20% than late administration.

Specific Aim 2: Determine the safety of insulin glargine 0.4 unit/kg early administration within four hours from IV Insulin infusion initiation.

III. METHODS

A. Study Design and Methodology:

This will be a prospective, open-label, intervention cohort study including all consecutive adult patients with Diabetes Ketoacidosis (DKA) getting admitted to Fairview Hospital-Medical Intensive Care Unit (FV-MICU). Screening of patient eligibility and informed consent will be done by the MICU admitting physician once the patient gets admitted to MICU. Participants will be given an overview of the study, including study procedures, and potential risks. Participants will be given adequate time to review the consent form and have opportunities to ask questions. After the informed consent process has been completed and a consent form has been signed, a copy of the consent will be provided to the participant and another copy will be secured in the Principle Investigator office in a locked cabinet. Enrolled participants in the intervention group will receive an Insulin Glargine 0.4 Unit/kg within 4 hours from initiating the IV Insulin Infusion, as per the Cleveland Clinic DKA protocol. The remaining of the management will be following the CC DKA protocol including continuing IVII till Anion Gap Closure (AG ≤ 12), Basal Metabolic Panel Q 2 hrs, and replacing electrolytes as indicated. After closing the anion gap, the decision for giving more Basal Insulin doses will be left to the treating physician's discretion. For patient safety, Point Of Care (POC) blood glucose will be checked hourly before IVII discontinuation. After IVII discontinuation, the BG will be checked with meals, bedtime and 2 am if the patient maintain good oral intake, if not, the BG will be checked q 4 hrs. Target BG 150 – 200 mg/dl during the DKA management and 140 – 180 mg/dl after DKA resolution as per American Diabetes Association recommendations. In case of any hypoglycemia event, this goal will be achieved by using Dextrose containing fluid or carbohydrate enriched oral intake which will be left to the treating physician discretion depending on patient awareness and severity of hypoglycemia. Also, the pre meals and correctional insulin doses after AG closure will be left to the treating physician's discretion. After AG closure the pre meals and correctional insulin doses will be left to the treating physician's discretion. In case of not closing the AG after 24 hours from the initial Glargine dose, the decision for further Glargine doses will be left to the treating physician's discretion.

The investigator team will be notified by the MICU attending after each participant enrollment, so one of the team members will present to MICU to collect the data prospectively in a standardized Data Collecting Sheet (DCS) by using REDCap and all protected health information (PHI) will be de-identified. As regards the control group, an E-research request will be submitted to provide a list by

all the consecutive adult patients admitted to FV-MICU with a diagnosis of DKA in the period between January 1st 2019 till the date of IRB approval. Prespecified sample size and matched in basal patient characteristics and DKA severity will be selected as the control group. Data will be collected retrospectively for the control group and will be recorded directly into the DCS in RedCap. Clinical outcomes will be compared between the intervention and control groups. The primary outcome includes time to anion gap closure (AG ≤ 12). Secondary outcomes include hospital Length Of Stay (LOS), ICU LOS, total IVII dose, the incidence of transitional failure (defined recurrence of DKA after initial IVII discontinuation within 24 hours and requiring reinitiating the IVII), the incidence of hyperglycemia (> 180 mg/dL) and hypoglycemia (defined as ≤ 70 mg/dL, <54, <40) during 24 hours from Insulin Glargine administration.

B. Definition of main exposures and outcomes:

Diagnosis of DKA will be made by ICD-10-CM code E10.10, E11.10, or meeting the ADA definition; BG ≥ 250 mg/dl, AG > 12, and positive Ketones in serum or urine

DKA classification as the following table from ADA:

	Mild (plasma glucose >250 mg/dl)	Moderate (plasma glucose >250 mg/dl)	Severe (plasma glucose >250 mg/dl)
Arterial pH	7.25–7.30	7.00 to <7.24	<7.00
Serum bicarbonate (mEq/l)	15–18	10 to <15	<10

For the hyperglycemia analysis, patients will be compared in the following categories according to their mean or median (depending on the normality of the data distribution) blood glucose throughout the hospital stay:

- Mean/median BG <80 mg/dL
- Mean/median BG 81-100 mg/dL
- Mean/median BG 101-140 mg/dL
- Mean/median BG 141-180 mg/dL
- Mean/median BG > 180 mg/dL'
- Mean/median BG > 240 mg/dL

Hypoglycemia will be defined by three categories:

- any glucose level below 70 mg/dL
- any glucose level less than 54 mg/dL
- any glucose level less than 40 mg/dL

For Time of Anion Gap Closure (TAGC) will use the ADA definition: AG ≤ 12 mEq/L

Transitional failure will be defined as the recurrence of DKA (BG ≥ 250 mg/dl, AG > 12, and positive Ketones in serum or urine) after initial IVII discontinuation within 24 hours and requiring reinitiating the IVII.

C. Study Population

Intervention vs Control group

- Intervention group: All consecutive adult patients getting admitted to FV- MICU and meet the inclusion criteria and accepted to receive insulin glargine early as per the protocol. They will receive insulin glargine 0.4 unit/kg within 4 hours from initiating the IV Insulin Infusion, as per the Cleveland Clinic DKA protocol.

- Control group: prespecified and matched sample size, consecutive adults who admitted to FV-MICU with a diagnosis of DKA in the period between January 1st 2019 till the IRB approval date and didn't receive basal insulin before AG closure.

Inclusion criteria:

- Age ≥ 18 years old
- Meet DKA definition as above
- Having the capacity to sign Informed consent

Exclusion Criteria

- IV insulin infusion initiated more than 4 hours.
- Persistent hypotension (SBP<80 mmHg despite receiving 1000cc normal saline).
- Require Vasopressor
- Acute Coronary Syndrome
- Pregnant
- End-stage renal disease
- Unwilling to consent to participate in the trial
- Currently under police custody
- Transferred from another hospital
- Require emergent surgery
- Alcoholic Ketoacidosis

Study Variables:

General Informations:

- Patient name
- MRN
- Age
- Sex (Male, Female, Others)
- Race (White, Black, Asian, Other)
- Ethnicity (Hispanic vs. Non-Hispanic)
- Weight on admission (kg)
- BMI (Kg/m^2)
- Height (cm)
- Date of Hospital admission
- Date of ICU admission

- Date of DKA diagnosis (MM/DD/YY)
- Precipitating cause of DKA
    - Noncompliance
    - New-onset
    - Infection
    - Cerebrovascular accident
    - alcohol abuse
    - pancreatitis
    - Drugs
    - Others

Past Medical history

- Type of diabetes:
    - Type 1 DM
    - Type 2 DM
    - Cystic fibrosis-related diabetes
    - Steroid-induced diabetes
    - Other or no clear diagnosis
- Known diagnosis of other major medical comorbidities (CAD, CHF, HTN, COPD, asthma, liver disease, CKD, cancer, other)
- On Renal Replacement Therapy (Y/N)
- Using Basal insulin at home (Yes/No/ unknown)
- If previous point answer is yes check the corresponding insulin type and write the dose: (Glargine, Detemir, Degludec, NPH, Continous Insulin Pump) (dose: IU)
- Home total basal insulin dose (units)
- Non-insulin antihyperglycemics taken at home prior to admission, including the type
    - Sulfonylureas
    - Thiazolidinediones
    - Dipeptidyl peptidase-4 (DPP-4) inhibitors
    - Biguanides
    - Glucagon like peptide-1 (GLP-1) analogues
    - Sodium-glucose transport protein 2 (SGLT2) inhibitors
    - Meglitinides
    - Alpha glucosidase inhibitors
    - Amylin analogues

- History of immunosuppression (history of cancer, HIV or auto-immune disease or organ transplant, chronic steroid)

Initial Laboratory values:

- Anion gap (mEq/L)
- Bicarbonate (mEq/L)
- Glucose (mg/dL)
- Beta-Hydroxybeutrate (mmol/L)
- Ketones in the urine (Y/N/Unknown)
- HbA1c %
- Lactate (mmol/L)

Intervention and outcomes:

- IV insulin infusion starting time
- Insulin glargine administration time
- Anion Gap closure time
- IV insulin discontinuation time
- Number of hours of IVII
- Total IV insulin infusion has been given
- Total IV insulin/weight
- Total IV fluid during DKA management
- Date of discharge from ICU
- Date of discharge from hospital
- Hospital Length Of Stay (days)
- ICU LOS (hours)
- Transitional failure (recurrence of DKA)?

Hypoglycemia Events

- Hypoglycemia event within 24 hrs from glargine
- Time of the hypoglycemia
- How many hours after the glargine administration?
- Severity
- How it has been treated

Hyperglycemia Events

- Hyperglycemia Event after IVII discontinuation by 24 hours (Y/N)
- time of the hyperglycemia event
- Severity of hyperglycemia
- How many hours after IVII discontinuation

D. Outcomes

Primary outcome: Time to anion gap closure (hours).

Secondary outcomes:

- Hospital Length of stay (days)
- ICU length of stay (hours)
- Total IV insulin infusion dose (International unit)
- Incidence of transitional failure (percentage).
- Incidence of hyperglycemia (> 180 mg/dL) during 24 hours from Insulin Glargine administration (percentage).
- Incidence of hypoglycemia (defined as ≤ 70 mg/dL, <54, <40) during 24 hours from Insulin Glargine administration (percentage).

IV. DATA COLLECTION

For the control group, the data will be collected retrospectively and recorded in standardized DCS in RedCap. For the intervention group, the data will be collected prospectively by the investigator team members and observations will be recorded in standardized DCS in RedCap. All protected health information (PHI) will be de-identified for both intervention and control group by using de-identification function in REDCap.

V. DATA ANALYSIS

The sample size calculation considered the average time of AG closure in the last 3 months in FV-MICU was 15.6 ± 2.5 hours (CI 95%) and SD of 6 hours. Using one-sided α of 0.025 and an β of 0.10, an expected 20% difference between the two groups, a sample size of 160 totally of the participant will be adequate.

Categorical variables will be described as frequency rates and percentages, and continuous variables will be described using mean, median, and interquartile range (IQR). Proportions for categorical variables will be compared by Chi-squared test of Fisher's exact test. Means for continuous variables will be compared by Student's t-test if normally distributed and Mann-Whitney test if not normally distributed. All statistical analyses will be performed with a one-sided p-value < 0.025 to determine statistical significance. All statistical analyses will be completed by study investigators using Statistical Analysis Software (SAS).

VI. DATA AND SAFETY MONITORING PLAN (if applicable)

All data will be stored in a secured REDcap database. No PHI will be saved on non-HIPAA protected devices. All protected health information (PHI) will be de-identified by using RedCap.

To ensure patient safety, CCF Hypoglecmia protocol is getting followed in all patients receiving insulin including our enrolled participants. Before IV insulin discontinuation, the blood glucose level is getting checked hourly as per protocol. Once the AG is closed and insulin infusion is discontinued, the patient who is maintaining oral intake, blood glucose will be checked with meals, bedtime, and 2 am. If the patient having poor oral intake, blood glucose will be checked q 4 hours. Different treatment options for any hypoglycemic events are available in the protocol depending on the severity of the hypoglycemia event and patient awareness, ranging from oral carbohydrate supplement to IV fluid containing dextrose.

VII. STUDY LIMITATIONS

- Retrospective EPIC data review for the control group. Single-center.

VIII. ETHICAL CONSIDERATIONS

For patient safety, insulin therapy is carrying a risk of hypoglycemia events. Previous studies didn't show any additional risk when insulin glargine has been given before anion gap closure comparing to the common practice, after anion gap closure. Shankar and Hsia's studies (4, 8) didn't reveal any hypoglycemic events between both groups. Both Doshi and Houshyar's studies (6, 7) revealed similar hypoglycemic events between both intervention and control groups and were neither clinically nor statistically significant.

The possible explanation for that is although the overlap time of glargine and IV insulin infusion is longer in the intervention group, the insulin infusion rate is getting adjusted hourly to meet the body requirement to decrease the blood sugar by a range of 50 - 100 mg/dl per hour. To ensure patient safety, CCF Hypoglecmia protocol is getting followed in all patients receiving insulin including our enrolled participants. Before IV insulin discontinuation, the blood glucose level is getting checked hourly as per protocol. Once the AG is closed and insulin infusion is discontinued, the patient who is maintaining oral intake, blood glucose will be checked with meals, bedtime, and 2 am. If the patient having poor oral intake, blood glucose will be checked q 4 hours. Different treatment options for any hypoglycemic events are available in the protocol depending on the severity of the hypoglycemia event and patient awareness, ranging from oral carbohydrate supplement to IV fluid containing dextrose. After AG closure the pre meals and correctional insulin doses will be left to the treating physician's discretion.

For data safety, all data will remain anonymous, and no personal health information will be associated with any data resulting from this study. Data will recorded directly into a secure REDCap database. No PHI will be saved on non-HIPAA protected devices. All protected health information (PHI) will be de-identified by using RedCap.

All subjects will be provided a consent form describing this study and with sufficient information to make an informed decision about participation in the study. The consent form will be submitted with the protocol for review and approval by the IRB. The formal consent of a subject, using the IRB-

approved consent form, will be obtained before the subject undergoes any study procedure. This consent form must be signed by the subject, and the investigator-designated research staff obtaining the consent.

The study will be conducted following ethical principles founded in the Declaration of Helsinki. The IRB will review all appropriate study documentation to safeguard the rights, safety, and well-being of the patients. The study will only be conducted at sites where IRB approval has been obtained. The protocol, informed consent, written information given to the patients, safety updates, progress reports, and any revisions to these documents will be provided to the IRB by the investigator.

IX. PLANS FOR DISSEMINATION OF FINDINGS

The goal of this study is to present the findings at a national scale meeting and to eventually publish a manuscript in a PubMed indexed journal.

XI. APPENDICES

Data Collecting Sheet

X. REFERENCES

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