Summary

Diabetic ketoacidosis (DKA) is a medical emergency that is associated with significant morbidity and mortality for both patients with type I and type II diabetes[1]. DKA is diagnosed with a blood glucose level > 250 mg/dL, pH </= 7.3, sodium bicarbonate level of </= 18 mEq/L, an anion gap > 10, and the presence of urine and/or serum ketones. Insulin is one of the main treatment modalities for DKA. By correcting hyperglycemia and inhibiting the release of free fatty acids, insulin administration leads to decreased ketone formation and resolution of acidosis. Short-acting (Regular) intravenous insulin is often preferred to subcutaneous administration for initial management due to its short half-life and ease of titration, but patients will eventually need to transition to subcutaneous insulin prior to discharge[1]. This transition will likely include the administration of long-acting, basal insulins such as insulin glargine (Semglee®, Lantus® or Basaglar®) or insulin deguldec (Tresiba®), which have a slow onset of action and have an extended duration of action[2]. The timing of initiation or resumption of home long-acting subcutaneous insulin is controversial in the treatment of DKA. Traditionally, patients are transitioned from IV to subcutaneous insulin once the patient reaches a blood glucose level of < 200 - 250 mg/dl and experiences two of the following: anion gap closure (≤ 12 mEq/L), resolution of acidosis (pH > 7.3), and/or a sodium bicarbonate level of ≥ 15 mEq/L[1]. The 2019 American Diabetes Association Standards of Medical Care in Diabetes recommend initiation of basal insulin 2 – 4 hours prior to discontinuation of intravenous insulin[3]. However, the 2014 Joint British Diabetes Societies Inpatient Care Group on The Management of Diabetic Ketoacidosis in Adults, recommend continuing patient's subcutaneous basal insulin during the initial management of DKA[4].

Small prospective, randomized, controlled, pilot trials have shown early initiation of basal insulin within 2-12 hours of IV insulin infusion initiation can prevent rebound hyperglycemia when the insulin infusion is eventually discontinued. These trials have also shown trends toward decreased time to anion gap closure, resolution of acidosis, and hospital length of stay with no increase in hypoglycemic events[5–7]. Retrospective studies have also shown decreases in time on insulin infusion and trends toward shorter ICU length of stay, resulting in lower costs to the institution[8]. The optimal dose and initial timing of early basal insulin is unknown. Trials have used initial basal insulin dosing ranging from 0.25 to 0.4 units per kilogram that was initiated anywhere from 2 to 12 hours after the initiation of IV insulin infusion, but no prospective trials have examined resuming the patient's home basal insulin early in the course of DKA treatment [5–7].

It is currently unknown if resuming a portion or all of the patient's home basal regimen during the initial treatment phase of DKA will provide an impact on patient care. The objective of this study is to evaluate the impact of early glargine administration at a dose of 0.2 units/kg if the patient was not previously on basal insulin or resuming the patient's home basal insulin regimen within two hours after the start of the intravenous insulin infusion in addition to usual care. We will conduct a prospective, randomized study comparing initiation early glargine administration to current standards of care. Outcomes include patient length of hospitalization, ICU length of stay, time to resolution of acidosis and anion gap closure, incidence of hypoglycemia, and incidence of rebound hyperglycemia.

One of the major benefits of this study is its utter simplicity. We will only have one intervention, and only in the intervention group (starting long-acting insulin early along with IV insulin therapy). The control group (standard of care group (SOC)) will be treated as they have been historically using the Regions Hospital DKA treatment protocol. We are not asking for more labs or nursing/provider interventions than usual. We are also not asking more of our pharmacists besides making at most 1-2 more doses of long-acting insulin for patients in the intervention group. This small intervention can help reduce ICU and hospital LOS, time on IV insulin infusion, and total amount of IV insulin administered- all of which will lead to a much greater cost reduction than 1-2 extra doses of long-acting insulin. As an added bonus, per preliminary reports (discussed below) giving long-acting insulin along with the IV insulin infusion does not lead to any additional adverse events, including hypoglycemia.

Study aims

Primary Outcome:

1) Does early administration of insulin glargine result in a shorter ICU length of stay when compared to usual care for the treatment of diabetic ketoacidosis?

   Hypothesis: Early administration of insulin glargine will result in shorter ICU length of stay when compared to usual care in patients with DKA.

Secondary Outcomes:

1) Does early administration of insulin glargine result in a shorter hospital length of stay (defined as time between start of insulin infusion and discharge from hospital) when compared to usual care for the treatment of diabetic ketoacidosis?

Hypothesis: Early administration of insulin glargine will result in shorter hospital length of stay when compared to usual care in patients with DKA.

2) Does early administration of insulin glargine result in a faster recovery from DKA (defined as blood glucose < 200 and two of: Anion Gap </= 12, Serum Bicarbonate ≥ 15 mEq/L, or pH > 7.3) when compared to usual care for the treatment of diabetic ketoacidosis?

   Hypothesis: Early administration of insulin glargine will result in a faster recovery from DKA (defined as blood glucose <200 and two of: Anion Gap </= 12, Serum Bicarbonate ≥ 15 mEq/L, or pH > 7.3) when compared to usual care for the treatment of diabetic ketoacidosis.

3) Does early administration of insulin glargine result in a shorter duration of elevated anion gap (defined as time with anion gap > 12) when compared to usual care for the treatment of diabetic ketoacidosis?

   Hypothesis: Early administration of insulin glargine will result in a shorter duration of elevated anion gap (defined as time with anion gap > 12) when compared to usual care for the treatment of diabetic ketoacidosis.

4) Does early administration of insulin glargine result in a shorter duration of time on IV insulin infusion when compared to usual care for the treatment of diabetic ketoacidosis?

   Hypothesis: Early administration of insulin glargine will result in a shorter duration of time on IV insulin infusion when compared to usual care for the treatment of diabetic ketoacidosis.

5) Does early administration of insulin glargine result in a lower prevalence of rebound hyperglycemia, defined as blood glucose > 180 mg/dL in the 24 hours after IV insulin infusion discontinuation, when compared to usual care for the treatment of diabetic ketoacidosis?

   Hypothesis: Early administration of insulin glargine will result in a lower incidence of rebound hyperglycemia, defined as blood glucose > 180 mg/dL in the 24 hours after IV insulin infusion discontinuation, when compared to usual care for the treatment of diabetic ketoacidosis?

6) What is the prevalence of a hypoglycemic (defined as blood glucose < 70mg/dL) event occurring while on IV insulin therapy or in the 24h hours after IV insulin infusion discontinuation with early insulin glargine administration compared to usual care?

   Hypothesis: The occurrence of a hypoglycemic event occurring while on IV insulin therapy or in the 24h hours after IV insulin infusion discontinuation with administration of insulin glargine is comparable to usual care.

7) Does early administration of insulin glargine result in a statistically lower mean blood glucose value in the 24 hours and (separately) 48 hours after IV insulin infusion discontinuation?

   Hypothesis: Early administration of insulin glargine will result in a lower mean value of blood glucose in the 24 and 48 hours after IV insulin infusion discontinuation.

Background, Rationale, Significance

In 2014, there were 168,000 hospitalizations for DKA, and the average length of stay was 3.4 days in 2009[1]. The estimated annual direct medical expense and indirect cost is 2.4 billion dollars per year[1]. DKA is a potentially life-threatening condition due to its ability to cause metabolic acidosis, electrolyte imbalances, and dehydration[1]. While DKA treatment protocols differ from institution to institution, the goals of treatment remain the same --- resolution of acidosis, dehydration, and hyperglycemia. Following fluid resuscitation, correction of hyperglycemia with insulin therapy is the mainstay of treatment[11]. Intravenous (IV) insulin infusions with regular insulin are commonly used due to its short half-life of 30 to 60 minutes and resulting titratability[1]. Treatment is then continued with subcutaneous (SC) insulin once the acidosis and anion gaps have cleared and the patient's hemodynamics and electrolytes abnormalities have resolved[3]. At Regions Hospital, the current criteria for transitioning from IV to SC insulin include meeting the following criteria: 1) fasting blood glucose levels are stable between 180-250 mg/dL for at least 4 hours, 2) vital signs, potassium, and sodium levels are stable and within the normal range, 3) the metabolic acidosis has cleared (anion

gap <15, and either arterial pH ≥ 7.3 or venous pH ≥ 7.27), and 4) the patient is able to eat regular meals. Traditionally, when SC insulin is initiated, the IV insulin infusion is stopped two hours later. However, the timing of SC initiation has becoming more controversial in recent years. The 2019 American Diabetes Association Standards of Care recommend transition of patients from IV to SC insulin requires administration of basal insulin 2–4 h prior to the intravenous insulin being stopped to prevent recurrence of ketoacidosis and rebound hyperglycemia[4]. However, the 2014 Joint British Diabetes Societies Inpatient Care Group recommend continuing a patient's home basal insulin during the initial management of DKA to prevent rebound hyperglycemia and to avoid extending length of stay[5]. Several recent papers have examined early basal insulin administration as adjunct therapies with IV insulin infusions for the treatment of hyperglycemia and DKA.

In 2012, a single-center prospective, randomized controlled trial by Hsia et al. compared IV insulin infusion with or without early administration of insulin glargine (dose = 0.25 U/kg) in 61 hyperglycemic patients with diabetes. Forty-one percent (25/61) of the patients enrolled in the trial were admitted with DKA. Those in the early insulin glargine arm were to receive the glargine subcutaneous injection within 12 hours of initiation of IV insulin infusion. Patients were excluded if they were newly diagnosed with hyperglycemia, critically ill, or pregnant. All other decisions about transitioning study subjects to SC insulin was left to primary teams including dose, type of insulin, and timing of transition. Those patients that received early glargine had lower prevalence of rebound hyperglycemia when the insulin infusion was discontinued (experimental group: 33% vs control group: 93.5%; P < 0.001). The total length of IV insulin infusion was similar in the two groups (control group: 35 ± 13h vs experimental group: 42 ± 24h). The mean blood glucose levels within the 12-hour study period were significantly lower in the intervention group, while there were 3 asymptomatic hypoglycemic measurements in the control group and none in the intervention group[6].

In 2015, Doshi et al. conducted a two-center prospective, randomized controlled trial of 40 patients admitted for DKA. Patients were randomized to receive early insulin glargine (dose = 0.3 U/kg) or no glargine in addition to regular care. Those in the early insulin glargine arm were to receive the glargine subcutaneous injection within 2 hours of diagnosis. Patients were excluded if they required inotropic/vasopressor resuscitation, had ESRD, required emergent surgery, or were less than 18 years old, pregnant, unwilling to participate, prisoners, or transferred to another hospital. Patients in the control group were given insulin glargine once the anion gap closed and the IV insulin infusion was continued for two additional hours. There was no difference in time to anion gap closure (control group: 11.6 ± 6.4h vs experimental group: 10.2 ± 6.8 hours; p = 0.63), hospital length of stay (control group: 4.6 ± 3.6 days vs experimental group: 3.9 ± 3.4 days; p = 0.66), ICU admissions (control group: 4 admissions vs experimental group: 6 admissions; p = 0.71), ICU length of stay (control group: 1.2 days vs experimental group: 1.8 days; p = 0.47), and hypoglycemic events (control group: 3 events vs experimental group: 2 events)[5–8].

Also in 2015, Houshyar et al. conducted a single-center, prospective, randomized controlled trial of 40 patients admitted for DKA. Patients were randomized to receive early insulin glargine (dose = 0.4 U/kg) or no insulin glargine in addition to usual care. Those in the early insulin glargine arm were to receive the glargine subcutaneous injection within 3 hours of IV insulin infusion initiation. Patients were excluded if they had hypotension (systolic blood pressure < 80 mmHg despite receiving 1000ml NS), acute MI, progressive renal or hepatic failure, or lack of consent. Patients in the control group were given insulin glargine once the anion gap closed. There was no difference in duration of acidosis (control group: 16.91 ± 6.5h vs experimental group: 13.77 ± 6.1h; p = 0.123). There were higher rates of hyperglycemia following discontinuation of the insulin infusion in those that did not receive early glargine (51% vs. 35% of measurements in the experimental group showed a glucose >8.3 mM or >150 mg/dL; p = 0.046). There was no difference in hospital length of stay (control group: 5.9 ± 2.2 days vs experimental group: 5.1± 1.9 days; p = 0.225) or rates of hypoglycemia (control group: 7 events in 5 patients vs experimental group: 4 events in 4 patients; no p-value reported).

Lastly, Rappaport et al. (2019) conducted a single-center, retrospective cohort study of 106 admissions for DKA comparing early vs late initiation of basal insulin. Patients admitted to the MICU who were treated with home-dose basal insulin prior to DKA resolution and within 24 hours of IV insulin infusion initiation (n = 33) were compared to patients who were initiated on basal insulin within 6 hours before or any time after IV insulin infusion discontinuation (n = 73). Transition from IV insulin infusion to subcutaneous insulin was not addressed in a protocol and was left to the discretion of the provider. Patients were excluded if they had surgery within 48 hours of IV insulin infusion, were pregnant, were in vasopressor dependent shock, or had another indication for insulin therapy. Patients in the early group had initial daily doses of basal insulin of 0.48 U/kg (IQR: 0.34 – 0.62) compared to 0.44 U/kg in the late group. Patients in the early insulin group had their first dose of basal insulin 2.5 hours (IQR: 0.4 – 6.4) after IV insulin infusion initiation. There was no difference in transitional failure (early group: 6% vs late: 10%; p = 0.717), rebound hyperglycemia (early: 81% vs late: 88%; OR: 0.59, CI: 0.16 – 2.25), hypoglycemia events (early: 33% vs late: 55%; OR: 0.41, CI: 0.16-1.05); time to anion gap closure: (early: 7.8h vs late: 9.1h; p = 0.73), length of ICU stay (early: 34h vs late: 33.3h, p = 0.83), or hospital length of stay (early: 2 days vs late: 2 days, p = 0.9). There was a statistically significant decrease for time on IV insulin infusion (early: 13.8h vs late: 17.1h, p = 0.04).

Preliminary research at Regions Hospital determined that in 40 randomly selected patients admitted for DKA in 2019, the mean dose of basal insulin initiated was 0.39 units per kilogram, and it was administered a mean of 22.4 hours after initiation of the IV insulin infusion and 1.86 hours prior before discontinuation of IV insulin, which is consistent with ADA recommendations[1,3]

In summary, previous randomized studies using weight based basal insulin doses have shown that the early initiation of basal insulin can prevent rebound hyperglycemia with no increase in hypoglycemia. One retrospective study demonstrated a decrease of time on IV insulin infusion in those that received early basal insulin when compared to those that did not. These studies have also shown trends toward shorter ICU and hospital length of stay, anion gap closure, and time to resolution of acidosis but none have demonstrated statistical significance. However, no prospective trials have examined resuming the patient's home basal insulin early in the course of DKA[5–7]. It is currently unknown if resuming a portion or the entirety of the patient's home basal regimen will provide an impact on patient care. By conducting a prospective study comparing initiation of early glargine administration at the patient's home dose to current standards of care, early administration may lead to shorter ICU and hospital lengths of stay as well as shorter duration of acidosis. This could provide significant cost-savings to the institution and benefit patients in need of treatment for this serious complication of diabetes.

Approach

Study design

This is a prospective, randomized trial to determine whether a fixed dose of early basal insulin administration is superior to standard of care for the treatment of DKA.

Population

Inclusion Criteria

- Presented to Regions Hospital ED for chief complaint of DKA, nausea, vomiting, abdominal pain, hyperglycemia, or similar
- Meets all below diagnostic criteria for DKA per the American Diabetes Association:
    - Arterial or venous pH </= 7.3
    - Serum Bicarbonate </= 18 mEq/L
    - Ketonuria or ketonemia
    - Anion Gap > 10
    - Blood sugar > 250 mg/dL
- Receiving IV insulin infusion
- It is feasible to provide insulin glargine within 2 hours (+/- 30 minutes) of IV infusion start
- Will be admitted to the ICU for DKA, or already admitted to the ICU for DKA
- Ability to provide informed consent

Exclusion Criteria

- Age < 18
- End stage renal disease or hepatic disease
- Hypotension requiring IV vasopressors or inotropes at any point during admission (i.e. norepinephrine, dobutamine, vasopressin, etc.)
- Need for emergent surgery
- Pregnant patients
- Prisoners
- Indication for insulin therapy other than DKA (hypertriglyceridemia, beta-blocker overdose, hyperglycemia without DKA)
- Patients receiving prior to admission insulin pump therapy
- Patients receiving prior to admission combination insulin products (i.e. Novolin® 70/30, Novolog® 70/30, Humalog® 75/25, etc.)
- Did not consent to study

Sample size

From 1/1/2018 to 6/30/2019 there were 399 unique encounters of patients admitted to Regions Hospital with an associated ICD-10 code of E10.10 (Type 1 diabetes mellitus with ketoacidosis without coma), E10.11 (Type 1 diabetes mellitus with ketoacidosis with coma), E11.10 (Type 2 diabetes mellitus with ketoacidosis without coma),

E11.11 (Type 2 diabetes mellitus with ketoacidosis with coma), E13.10 (Other specified diabetes mellitus with ketoacidosis without coma), or E13.11 (Other specified diabetes mellitus with ketoacidosis with coma).

We expect patients to present at the same rate, indicating that an estimated 264 patients with one of these eligible diagnoses will present over the twelve months of study enrollment. Of those 264, we expect 25% to be ineligible due to meeting one of the study exclusion criteria and another 25% to be eligible but decline participation. Therefore, we expect to see 132 total eligible subjects (66 in each randomization arm). Due to our fixed sample-size, in lieu of a traditional power analysis to determine the number of subjects needed to detect a difference between the group we plugged our fixed sample size into a power analysis and solved for length of stay.

We ran a power analysis using the same historical data used under the Sample size section of this proposal. Because we expect about 132 patients to be enrolled, we inspected length of stay (LOS) from the first 100 cases in our historical data. LOS is heavily right-skewed, so we log-transformed it to estimate detectible effect size. We used the "proc power" program in SAS 9.4, which has specifications for comparing two log-transformed means. In order to achieve 80% power to detect a true difference between two fixed groups of n=66, the ratio of logs would have to be about 1.31; when normalized, this translates to about 6.5 hours (alpha = 0.05, coefficient of variation =0.6). So, with our sample size, we estimate that the intervention would need to cause a 6.5-hour difference in average length of stay between groups in order for us to detect a difference 80% of the time.

Data collection process

Please see the section titled "Outcome/endpoint and other variable definitions, and instruments used" for a full description of this process.

Screening and Enrollment

Screening

Because CCRC research interns provide 24/7 ED coverage, and ED pharmacy is also covered 24/7, there is no restriction as to the time of day or day of week when enrollments can take place. However, to enhance investigator oversight, patients will only be enrolled when specific ED Pharmacists are on shift, who are the primary investigators. This includes Eric Berg, Adis Keric, and Lisa Manson. If those pharmacists are not at the site, the patient will not be enrolled.

ED pharmacists received an Epic alert any time a patient meeting DKA criteria is admitted to the ED. The pharmacist will alert the CCRC research intern to confirm inclusion/exclusion and approach the patient for study participation. CCRC interns will also watch the ED track board for patients admitted with a chief complaint of DKA, nausea, vomiting, abdominal pain, hyperglycemia, or similar. Alternatively, an ED pharmacist or attending physician will notify Research of a potential patient by calling the 24/7 intern bat phone.

Labs: in order to confirm inclusion/exclusion criteria, the patient will need to have had the following labs completed *(which are standard of care for any patient with DKA on the differential diagnosis. These are not extra labs that the study investigators want, rather, they will already be collected by any provider for any patient with presumed DKA):*

- Arterial or venous pH </= 7.3
- Serum Bicarbonate </= 18 mEq/L
- Presence of ketonuria or ketonemia (beta-hydroxybutyrate > 0.27 mmol/L)
- Anion Gap > 10
- Blood sugar > 250 mg/dL

All patients who present with symptoms of possible DKA should receive these labs under standard of care, per Regions Hospital DKA Protocol. Should any of these labs be missing, the patient will not be eligible for the study.

The research intern will confirm inclusion and exclusion criteria using a RedCap screening checklist, and obtain permission from the patient's attending to approach for study consent.

Consent

If fully eligible, research staff will approach the patient for consent, either by calling the patient's room phone, mobile phone, or entering the patient's room in appropriate PPE. (Please see the "Setting/Environment/Organizational

feasibility" section for COVID-19 safety information.) Since DKA can sometimes cause confusion, if a patient is deemed by the care team to be incapable of informed consent, a patient's legally authorized representative may be approached instead. The patient or LAR may sign the consent form either on paper or electronically in RedCap.

Randomization

An Excel file with rows numbered 1 through 150 will be populated with a randomization column. Using Excel randomization functions, a research staff member who will not be involved in consenting will assign either the number 1 (control) or 2 (intervention) to each row number, ensuring 75 of each are populated. We chose the number 150 based on the expected sample size of 132, plus extras in case of higher-than-expected enrollment. The research staff member will then black out (black highlight over black font) the randomization column, so other team members are blinded to future assignments. Upon consent of an eligible patient, research staff will enter subject information in the next available row, and randomization status will be unblinded by removing the black highlight for that row only.

Enrollment

Once the patient is randomized, the CCRC intern will notify the ED pharmacist who will determine if patient is currently taking basal insulin and, if they are taking basal insulin prior to admission, will verify the home basal dosing. CCRC research staff will be notified of the dosing order from the randomization and will place the appropriate order. The patient will either receive 0.2 u/kg insulin glargine, current (prior to admission) basal insulin dose, or no additional treatment study protocol. CCRC staff will abstract the study data points from the patient's EMR while the patient is in the Emergency Department, throughout their hospital stay, and again at the time of discharge. The ED pharmacist will time the insulin glargine dose to be administered optimally within two hours after initiation of the IV insulin infusion.

Interventions and Treatments

Intervention group-specific

For patients who are randomized to the intervention group, subcutaneous insulin will be ordered as follows:

Prior to administration basal insulin (generic)	Prior to administration basal insulin (brand)	Dose equivalent of insulin glargine
Insulin glargine	Lantus; Basaglar, Semglee	1:1
Insulin degludec	Tresiba	1:1
Insulin detemir	Levemir	1:1
None	None	0.2 units/kg

If the patient is in the intervention group, the ED pharmacist and/or research intern will determine if the patient was taking basal insulin prior to admission. If the patient was not taking basal insulin prior to admission, the patient will receive 0.2 units/kg insulin glargine. If the patient was taking basal insulin prior to admission, the patient will receive their home insulin glargine dose.

Once the appropriate dose is determined, the research team will order the randomization dose of study medication and the ED pharmacist will time the study medication to begin within 2 hours after initiation of the IV insulin infusion. The dose will come from IV pharmacy and dispensed in a 1 mL insulin syringe. These syringes are then tubed to the ED.CCRC interns may facilitate this process by picking up the dose from the ED pharmacy or watching the tube stations closely for the dose to arrive, as nurses are sometimes too busy to check these stations on a regular basis. Once the insulin is provided, the nurse will administer the dose. Since the dose if not on basal insulin at baseline is weight-based, a current weight will be taken if not already done at admission. Research staff will ask the RN to complete this.

Research interns will complete follow-up evaluation of incidence of hypoglycemia or hyperglycemia after IV insulin infusion discontinuation. This step will be done in conjunction with one of the study investigators.

Control group-specific

If the patient is in the standard of care (control) group, no orders for SC insulin glargine will be placed for research purposes. A consent note and research FYI flag will be placed in the patient's EMR to alert care teams of study

participation and to emphasize the importance of adhering to the Regions Hospital DKA Protocol, namely, to not administer long-acting insulin until patient meets all criteria as per Regions Hospital DKA Protocol. In the intervention group, the patient will have all of the same labs and medications as they would if they were in the control group or if they were not in the study at all. If they are in the intervention group, the timing of SC insulin will be earlier than it would if the patient were not in the study, but all components of the protocol are identical regardless of arm or study participation.

Various measures will be taken to promote care team compliance with the hospital DKA protocol in the control group. These include education of ICU and ED providers, including pharmacists and RNs and careful instructions to follow the SOC protocol (with exceptions for the experimental arm) in the FYI flag and consent note. Furthermore, CCRC research interns will be involved in each enrollment to ensure that insulin glargine is given in the study time window and that SOC labs are completed per the DKA Protocol. Finally, ED pharmacists are on service 24 hours per day and will be available for study patient oversight.

Variable list, sources, and data collection

The variables listed on the below data collection form will be incorporated into a secure REDCap database that research staff will use to enter the data. Patients will be assigned study ID numbers in the REDCap database. The REDCap database will contain identifying information, however, if de-identified data needs to be shared outside of the direct study team, the dataset can be downloaded without identifying variables such as MRN.

Variable Name	**Role of Variable**	**Measurement Scale**
Study ID	Unique identifier	Continuous (001 – n)
MRN	Link to EMR	String
Full name	Link to EMR	String
Date of ED presentation	Link to EMR	DMY
Age	Descriptive	Continuous
Race	Descriptive	Categorical, as reported in Epic
Ethnicity	Descriptive	Categorical, as reported in Epic
Sex at birth	Descriptive	Categorical, as reported in Epic
End stage renal disease or hepatic disease	Inclusion/exclusion criteria	Binary
Vasopressor dose to treat hypotension at any point during admission	Inclusion/exclusion criteria	Binary
On insulin pump therapy at baseline (prior to ED)	Inclusion/exclusion criteria	Binary
On combination insulin products (i.e. Novolin® 70/30, Novolog® 70/30, Humalog® 75/25, etc.) at baseline	Inclusion/exclusion criteria	Binary
Presenting pH (prior to intervention)	Inclusion/exclusion criteria	Continuous

Time of first pH	Calculate time to resolution	Continuous
Time of short-acting insulin start	Calculate time to resolution	Continuous
Time of first pH > 7.3	Outcome Calculate time to resolution	Continuous
Presenting blood glucose in mg/dL	Inclusion/exclusion criteria	Continuous
Time of first blood glucose < 250 mg/dL	Outcome Calculate time to resolution	Continuous
Blood glucose > 180 mg/dL in the 24 hours after IV insulin infusion discontinuation	Outcome	Binary
Blood glucose < 70mg/dL ≥ 1 time at any point while on IV insulin therapy or in the 24 hours after IV insulin infusion discontinuation	Outcome Prevalence of AE (hypoglycemia)	Binary
Blood glucose < 70mg/dL at any point between glargine start and 24 hours after IV insulin infusion discontinuation (control group only)	Outcome Prevalence of AE that may be contributable to study intervention (hypoglycemia)	Binary
Mean blood glucose in 24 and 48 hours after IV insulin infusion discontinuation	Outcome	Continuous
Presenting anion gap	Inclusion/exclusion criteria	Continuous
Time of first anion gap	Calculate time to resolution	Continuous
Time of first anion gap < 12	Calculate time to resolution	Continuous
Presenting serum bicarbonate level in mEq/L	Inclusion/exclusion criteria	Continuous
Time of first serum bicarbonate < 15 mEq/L	Calculate time to resolution	Continuous
Presence of ketonuria or ketonemia on presentation	Inclusion/exclusion criteria	Binary
Presenting Beta-Hydroxybutyrate in mmol/L	Inclusion/exclusion criteria	Continuous

Type I or Type II Diabetes	Descriptive	Binary
Prior to admission history of current basal insulin usage	Treatment determination if in intervention arm	Binary
Home Insulin Dose	Treatment determination if in intervention arm	Continuous
Time of IV insulin infusion initiation	Ensure protocol compliance Start of outcome measure	Date/Time
Time of IV insulin infusion discontinuation	Outcome	Date/Time
Time of SC insulin glargine administration	Descriptive Ensure protocol compliance	Date/Time
Exact dose of SC insulin glargine administered	Descriptive Ensure protocol compliance	Date/Time
Weight in kg	Determine insulin glargine dose for study order	Continuous
Date/time of ICU admission	Calculate ICU LOS post-infusion for study outcome	Date/time
Date/time of ICU discharge (defined as time of service switch to progressive care or general medicine)	Calculate ICU LOS post-infusion for outcome	Date/time
Date/time of IV insulin infusion start	Calculate LOS post-infusion for study outcome	Date/time
Date/time of hospital discharge	Calculate LOS for study outcome	Date/time

Statistical analysis plan

The primary outcome and secondary outcomes 1-4 and 7 will follow the same analysis plan to study the difference in the distribution of time to an endpoint. First, the distributions for each of these outcomes will be evaluated to determine if the distribution is normal or non-parametric. If the distribution is normal, that outcome will be analyzed using a two-tailed unpaired t-test. If the distribution is non-parametric, that outcome will be analyzed using a Wilcoxen rank sum test. We expect length of stay data to follow a non-parametric distribution. In secondary outcome 2, the outcome measured is the time at which all of the necessary criteria are hit for the first time simultaneously, which accounts for the transient nature of some of these measures.

Secondary outcomes 5-6 will measure the prevalence of each of these outcomes. Prevalence was chosen over incidence in order to account for multiple instances of rebound hyperglycemia or hypoglycemia occurring within the specified timeframe for each and also the amount of time it takes to clinically reverse these conditions. For both of these outcomes, a two-proportion z test will be run to find the difference in the amount of time each treatment arm cumulatively spent with the specified condition. Finally, for the outcomes relying on certain lab values, we will examine time from IV insulin infusion start to outcome labs in both groups. If there is significant variability between the experimental and SOC arms, we will adjust for this statistically. Group randomization should ensure that variability is

equally distributed between groups, however, there is a chance of bias (e.g., if the experimental group fares better and thus are slower to get nursing checks.)

Strengths and limitations

One strength of this study includes the 24/7 availability of the CCRC Research Intern and the ED Clinical Pharmacist to assist with patient enrollment. This will allow patients to be enrolled on all shifts. The biggest strength in this study is the potential to provide a data set more than double the size of the previous studies on early basal insulin administration in DKA. This study will also follow the patient throughout their hospital stay and look at potential practice changes to decrease the overall length of stay for patients with DKA. We have worked with all relevant departments (ED, Critical Care, Endocrinology, Pharmacy) to ensure that this research will fit into the current workflow for DKA patients without impeding patient care.

The biggest limitation is that while our sample size is larger than the previous publications on this topic, it is still a small pilot study and effects will be somewhat limited to our local setting and practices. This is also a single-center study and not all Emergency Departments have 24/7 ED Clinical Pharmacists available so these practices may not be easily duplicated. Not all patients who are eligible will agree to be in the study, which may cause participation bias. To avoid research bias, a staff member who will not be involved in consent will set up the randomization scheme, so enrollers will be unaware of the next randomization assignment when they approach patients

Furthermore, since this is a pragmatic study in the real-world setting of a functioning, busy ED, research has limited control over components such as timing of standard of care labs and study intervention. We will report and statistically correct for any large variation in timing of outcome labs, such as post-intervention glucose checks.

Setting/Environment/Organizational feasibility

The study will be conducted at Regions Hospital. The study will primarily take place while the patient is in the ED, but the study intervention may take place in the ICU if the patient is quickly admitted. The ED pharmacists can oversee ICU medication orders, and the ICU pharmacists will also be trained about this study. This location is appropriate as this study is designed to assess the efficacy and safety of early basal insulin administration versus standard of care for the treatment of DKA. The department heads for endocrinology, emergency medicine, critical care, internal medicine and pharmacy were contacted and have endorsed providing support for this study. The Department of Endocrinology was consulted on providing recommendations for both the dosing of basal insulin as well as the timing of basal insulin initiation in relation to starting the IV insulin infusion. Furthermore, the ED pharmacists, ICU pharmacists, and floor pharmacists have a close working relationship, and communicate with each other daily. All three study investigators have spent time working as ICU pharmacists.

Due to the ongoing COVID-19 pandemic, additional actions will be taken to ensure the safety of patients and research staff. Research staff will follow the same PPE protocols as each patient's care team. Room entries for patient who have been ruled out for COVID will require a surgical mask. If a patient's COVID status is unknown, but COVID is not suspected, research staff will attempt to contact the patient via phone, or have a care team member who is entering the room for cares ask if the patient is interested in speaking with research, before entering the patient's room themselves. In this case, the research team will follow the same PPE routine as care team members who are entering the room. CCRC staff has permission to use PPE from the ED for research purposes. To reduce strain on ED PPE, CCRC staff has been instructed to retain N-95 masks and reuse for the equivalent of 5 full shifts per the current Worksite Health recommendation, and each CCRC staff member has their own reusable face shields. If the patient is COVID-positive, patients will not enter the patient's room, and will instead attempt to contact the patient via phone. If a paper consent form needs to be signed, a member of the care team in full PPE will bring it in to the patient at the time of other cares. Patients and LARs will be offered the option to sign a digital consent form, sent to their personal device via RedCap, as this will avoid a Research room entry.

Risks and Benefits

Potential risks to the patient include hypoglycemia with the administration of both basal and regular insulin administration, however, no study that has examined early basal insulin in combination with IV insulin has shown an increase in the risk of hypoglycemia[5–8]. Standard of care for patients with DKA includes an overlap of basal and regular insulin for approximately two hours; this ensures that the basal insulin has time to start working before stopping the regular insulin. In our study, patients will have a longer duration of overlap of basal and regular insulin as the basal insulin will be given earlier in the patient's treatment course. Patients with DKA who are receiving IV insulin

infusions, whether participating in this study or not, undergo frequent blood glucose monitoring and have the IV insulin infusion titrated appropriately to prevent hypoglycemia. Potential benefits to the patient and society include shorter hospital and ICU lengths of stay, faster time to resolution of DKA, and less rebound hyperglycemia.

For study patients randomized to the SOC group, the only potential for change in standard care would be if a provider who *would* have deviated from the Regions Hospital DKA Protocol were the patient not in the study *does not* deviate from it if the patient is in the study, due to education about the importance of adhering to the SOC DKA Protocol. (For example, a physician might give SC glargine before the patient meets all criteria for it in the DKA Protocol.) However, as the DKA Protocol is evidence-based, peer-reviewed, and created for optimal patient safety and outcomes, this should not be considered a risk. If, for whatever reason, a study patient in the SOC arm needs treatment that directly contradicts the SOC DKA Protocol, the patient will be withdrawn from the study to ensure patient care and safety are the first priority. In looking at existing data to inform this study protocol, only 3 of 45 patients with DKA at Regions Hospital received SC glargine prior to what the protocol dictates.

All adverse events and serious adverse events will be reported to the IRB within the required time windows.

Data Confidentiality and Privacy

This study involves only minimum necessary data Study results that are shared outside the study team will be de-identified and in aggregate form. Data will be entered and stored in an HP secure REDCap database, accessible only be study team members. All electronic identifiers will be destroyed from Regions Hospital computers at the time of study close-out.

Timeline

Milestones	2021								2022											
	M	J	J	A	S	O	N	D	J	F	M	A	M	J	J	A	S	O	N	D
- develop study protocol		x	x																	
- IRB approval process				x																
- enroll patients					x	x	x	x	x	x	x	x	x	x	x	x	x			
- data analysis																		x		
- draft publications																			X	X

Dissemination/Sharing Results/Integration and Impact

We plan to publish our results following study completion. The target journals include the American Journal of Emergency Medicine, Critical Care Medicine, and The Journal of Clinical Endocrinology & Metabolism. One of the ED pharmacists or pharmacy residents will be presenting preliminary results at the Midwest Pharmacy Residency Conference, to the pharmacy staff at Regions Hospital, and to the Emergency Medicine and Critical Care departments. Our goal is for the data to be incorporated in the development of future policy changes regarding the treatment of DKA.

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