BRISK-ED: Balanced crystalloids (RInger's lactate) versus normal Saline in adults with diabetic Ketoacidosis in the Emergency Department: a pilot randomized controlled trial

Principal Investigator:
Dr. Justin W. Yan, BSc (Hon), MD, MSc, FRCPC
Assistant Professor, Division of Emergency Medicine
London Health Sciences Centre 519-685-8500 ext. 55014

Co-Investigators:
Dr. Christopher Byrne, MD, MSc, FRCPC, Division of Emergency Medicine
Dr. Kristin K. Clemens, MD, Department of Medicine, Division of Endocrinology and Metabolism, Department of Epidemiology and Biostatistics
Dr. Naveen Poonai, MD, MSc, FRCPC, Department of Pediatrics/Medicine (Division of Emergency Medicine)/Epidemiology and Biostatistics
Dr. Yun-Hee Choi, PhD, Department of Epidemiology and Biostatistics
Ms. Haley Collins, Patient Partner, London Health Sciences Centre

Research Staff:
Erica Figgins, MSc, Division of Emergency Medicine, London Health Sciences Centre
Branka Vujcic, MSc, Division of Emergency Medicine, London Health Sciences Centre
Tom Chen, MSc, Division of Emergency Medicine, London Health Sciences Centre
Fardowsa Halane, BSc, Division of Emergency Medicine, London Health Sciences Centre

BACKGROUND AND SIGNIFICANCE

Diabetic ketoacidosis (DKA) is an acute, life-threatening complication of diabetes which requires treatment with intravenous (IV) fluid and insulin to correct hyperglycemia and reverse acidosis. Current DKA management guidelines recommend normal saline (0.9% sodium chloride) for resuscitation and treatment.[1-3] However, saline's chloride content is higher than that of human plasma and can cause a hyperchloremic metabolic acidosis, particularly when administered in large volumes (often needed in patients with DKA). Use of saline may thus worsen the clinical condition of patients who are already in an acidotic state.[4-7] Alternatives to saline are balanced crystalloids (e.g. Ringer's lactate-RL) which have chloride concentrations similar to human plasma; therefore, treatment with balanced crystalloids may lead to faster DKA resolution. One recent study (Self et al.) of emergency department (ED) patients presenting with DKA demonstrated that treatment with balanced crystalloids resulted in more rapid DKA resolution compared to saline (13.0 vs 16.9 hours, p=0.004).[8] While the difference in resolution time between groups was small, the authors suggested that "*consistent implementation of interventions that deliver small improvements in outcomes…can translate into substantial improvements in population health and health system function*." However, this study was single-centred, non-blinded, and was a post-hoc subgroup analysis of completed trials (i.e. SMART[9] and SALT-ED[10]) and power was not prospectively calculated. Other studies on this topic have been limited due to small sample sizes (45-77 patients) leading to low power with limited conclusions.[11-14]

STUDY OBJECTIVE(S); INCLUDING SPECIFIC AIMS AND/OR HYPOTHESES

We hypothesize that patients who are administered IV RL will have faster DKA resolution without a concomitant increase in adverse outcomes when compared with normal saline. However, a pilot randomized controlled trial (RCT) is necessary to assess the feasibility of a future multi-centre trial. Our specific objectives for this pilot study are to determine the feasibility of conducting a full-scale multi-centred RCT and to use this pilot data to inform the future trial.

METHODS

Design and Setting

This will be a single-centre, triple-blind pilot RCT evaluating the superiority of IV RL (intervention) compared to saline (comparator) in treating adult ED patients presenting with DKA over a one-year period. The study setting is London Health Sciences Centre (LHSC)'s Victoria Campus, an academic tertiary care centre with ~90,000 ED visits/year in London, Ontario. Study conduct will be in accordance with the CONSORT statement for pilot feasibility trials.[15]

Study Population – Inclusion/Exclusion Criteria

There are no definitive criteria for diagnosing DKA.[3] Thus, using the criteria employed by Self et al.[8] and the Diabetes Canada guidelines[3] we will include ED patients ≥18 years with a clinical diagnosis and laboratory values consistent with DKA, including:

- plasma glucose concentration ≥14mmol/L
- plasma bicarbonate concentration ≤18mmol/L and/or blood pH ≤7.30
- calculated anion gap >10mmol/L
- presence of ketones/beta-hydroxybutyrate in serum and/or urine

We will exclude patients who:

- Are initially seen at another ED and transferred to LHSC for care and/or admission
- Receive >1L of IV fluid prior to enrolment (e.g. pre-hospital by EMS or while waiting to be seen) – this may cause study contamination
- Are initially enrolled due to clinical suspicion of DKA based on elevated point-of-care glucose, but ultimately do not meet clinical/laboratory criteria for DKA (e.g. "hyperglycemia" only)
- Have euglycemic DKA (generally those on SGLT-2 inhibitors)

Study Procedures

Screening, Consent, and Enrolment

During weekday business hours (M-F 0700-1700), research assistants (RAs) will screen and identify eligible patients using our ED tracking board. They will approach the treating physician to confirm eligibility before discussing the study with the patient and seeking informed consent. Because the diagnosis of DKA requires laboratory confirmation, all patients with a point-of-care blood glucose confirming hyperglycemia (≥14mmol/L) will be approached for enrolment as a "possible DKA patient". If the treating physician agrees that DKA is possible and IV fluid is indicated, study fluid will be administered per the randomization protocol after consent is obtained. If patients are initially enrolled but the physician ultimately confirms they do not meet DKA criteria, they will be excluded from the analysis. During evening and weekend hours, RAs

will be available on-call, however nighttime coverage (after 2300h) will not be feasible for this pilot. After hours (and in the event our processes are affected by a prolonged COVID-19 pandemic), treating physicians can directly enroll patients as there will be study posters to outline enrolment processes and physicians will receive email and in-person reminders on study recruitment. We will review daily ED visit logs to identify missed patients to screen for bias.

Intervention and Comparator

The intervention is administration of IV Ringer's lactate and the comparator is administration of IV normal saline. Rate of study fluid will be at the treating physician's (both ED and inpatient, if consulted for admission) discretion. Apart from fluid administered, there will be no other changes to the patient's clinical care, and patients will receive standard DKA treatment which may include insulin, electrolyte replacement, and/or supportive management. Pharmacy-prepared kits of 8 x 1L bags of study fluid (in Self et al., a maximum of 7090mL was given[8]) will be kept in a secure space within the ED. Once packaged, IV bags are useable for 30 days before expiration. If a kit is opened but not used completely, individual 1L bags may be returned to the pharmacy to save on costs.

Randomization, Blinding, Allocation Concealment

Enrolled patients will be block randomized to treatment or comparator in a 1:1 allocation ratio. The block size will be unknown to investigators and those involved in patient care and will be small enough to ensure balance between each arm throughout the trial. The randomization list will be prepared by our pharmacy. The patients, treating physicians, and outcome assessors will be blinded to assigned treatment. Our pharmacy will prepare an opaque covering over each fluid bag within study kits, which will not be removed during the infusion to maintain blinding. Each bag will be labelled with a kit number and scannable bar code to ensure the patient receives study fluid as ordered which will be entered on their Medication Administration Record (Figure 1).

Figure 1. Image of Blinded Fluid Bag from Pharmacy

Study Outcomes

Primary Feasibility Outcome

The primary feasibility outcome is patient recruitment rate over the one-year study period. We will also measure adherence to the protocol for this pilot study. This pilot is not powered to determine differences in treatment groups; however, a priori outcome definition and accurate outcome assessment is needed to inform the future study.

Efficacy Outcomes

We also have efficacy outcomes consistent with those used by the previous study by Self et al.[8]:

> **Primary outcome:** time to DKA resolution (hours), defined as the time elapsed between ED presentation and ketoacidosis resolution, following criteria from the American Diabetes Association Consensus Statement on Hyperglycemic Crises1 (plasma glucose <11.1 mmol/L and two of: plasma bicarbonate ≥15mmol/L, venous pH >7.3 or anion gap ≤12mmol/L).

*Of note, Diabetes Canada's guidelines lack definitive criteria for DKA resolution, only stating that insulin infusion should continue until ketosis resolves (measured by "normalization of plasma anion gap").[3] Following Self et al.[8], patients discharged prior to evidence of laboratory criteria for DKA resolution will be classified as having DKA resolution at time of discharge.

> **Secondary outcomes:** time to insulin infusion discontinuation (hours), intensive care unit admission, in-hospital death, hospital length of stay (days), hyper- or hypokalemia (>6.0 or <3.0 mmol/L) post-ED, in-hospital acute kidney injury post-ED (Stage 2 or greater – defined as serum creatinine increase >200% from baseline or <0.5mL/kg/hr urine output for <12 hours) and major adverse kidney events within 30 days, defined as a composite of: i) death, ii) new renal replacement therapy, or iii) final serum creatinine ≥200% baseline at the earliest of hospital discharge or 30 days after ED presentation).

Our hospital's DKA protocol involves hourly point-of-care glucose checks and bloodwork (electrolytes, including anion gap, and venous blood gas) every two hours while receiving insulin infusions. Patient characteristics and clinical/laboratory data will be collected via our electronic medical record. All outcomes listed above can be ascertained via health records review, which will occur at 1,3,7, and 30 days post-enrolment.

Sample Size

The full-scale multi-centred will include 516 participants (258 per arm), assuming α=0.05, power=80%, 1:1 allocation, a 40% (6.76 hours) minimal clinically important reduction in DKA resolution time, and 10% attrition rate. This trial will be conducted at 6 ED sites over 2 years. Based on this, the sample size for this local pilot RCT is 52 participants (26 per arm).

Sample size for Full-Scale Trial

The sample size calculation for this trial was based on a study of Clinical Effects of Balanced Crystalloids vs Saline in Adults with Diabetic Ketoacidosis[8] which compared the clinical effects of balanced crystalloids with the clinical effects of saline for the acute treatment in DKA in two clinical trials (Isotonic Solutions and Major Adverse Renal Events Trial [SMART][9] and the

Saline Against Lactated Ringer's or Plasma-Lyte in the Emergency Department [SALT-ED]10). The primary outcome for this comparison was the time between ED presentation and DKA resolution, measured in hours. Self et al. (2020) found an absolute reduction in time to DKA resolution of 3.9 hours. In the balanced crystalloids group (n=94), the median time to resolution of DKA was 13.0 hrs [IQR: 9.5-18.8], while in the saline group (n=78) the median time to resolution was 16.9 hrs [IQR: 11.9-34.5]. The IQR was used to calculate the standard deviation for each group based on the following assumption for normally distributed data: SD=IQR/1.35. The pooled standard deviation was then calculated based on the sample size and standard deviation of each group from the Self et al. (2020) study [$\sqrt{((n1-1)*SD12 + (n2-1)*SD22)/(n1+n2-2))}$] and was determined to be 12.37. To establish superiority of balanced crystalloids versus saline in the time to resolution of DKA, a superiority margin for a clinically significant difference was chosen to be a 40% (=6.76 hours) reduction in time to resolution of DKA based on expert consensus and patient partner feedback. A conservative attrition rate of 10% was selected for the sample size calculation, as loss to follow-up rates should be low given the nature of the intervention (IV fluids) and follow-up period (<24 hours). The actual attrition rate determined by this pilot study will inform the sample size calculation for the full-scale multicentre study. Therefore, to achieve 80% power at the 5% level of significance with equal allocation, the sample size for the balanced crystalloids (Ringer's lactate) group and the saline group, while accounting for a 10% loss to follow up and a 25% reduction in time to DKA resolution, is 516 participants (258 per group). The sample size was calculated using Wang and Ji's (2020) method[16] for common clinical study designs available at http://riskcalc.org:3838/samplesize/.

We plan to conduct the full-scale trial at 6 ED sites over 2 years, which would require an average minimum recruitment of 86 participants per site (43 per site per year). Our research group has established relationships with these other Canadian EDs where we have previously conducted successful studies. If further sites are needed for recruitment, we will leverage the Network of Canadian Emergency Researchers (NCER).

Sample size for Pilot Trial

For the full-scale trial, a minimum of 43 participants must be recruited annually per site on average. The LHSC Victoria Campus ED treats approximately 130 patients with DKA annually, based on our hospital's Decision Support data from the most recent fiscal year (Mar 1 2019 – Feb 29 2020).

DKA by Site	Patients
Victoria Hospital	**130**
(E1010) Type 1 DM with ketoacidosis	70
(E1110) Type 2 DM with ketoacidosis	51
(E1112) Type 2 DM with keto & lactic acidosis	1
(E1410) Unspecified DM with ketoacidosis	8

Based on our research team hours of coverage (0700-2300) and past data from ED presentation time of potentially eligible patients, we expect to approach at least 104 (80%) of eligible patients in the one-year pilot study period, and a minimum of 43 approached participants (41.3%) must be recruited to meet the feasibility target. According to data from similar past trials, we

anticipate being able to recruit at least 50% of approached patients (target sample size of 52 patients, 26 in each arm). With 104 patients approached per year, a 90% two-sided confidence interval around the anticipated recruitment rate will have a total width of 0.17, i.e. a lower limit of 0.415 and an upper limit of 0.585. Because the lower limit excludes the minimum feasibility target of 41.3%, we can be 90% confident that the future trial is feasible.

DATA COLLECTION

Study data for each enrolled patient will be abstracted from the hospital's electronic medical records into the Lawson REDCap data storage platform. Study data will include minimal demographic information (e.g. sex, date of birth), the patient's medical history (e.g. comorbidities, medications), arrival ED information (e.g. CTAS, arrival vitals), hospital interventions (e.g. IV fluids administered), comprehensive bloodwork results, and discharge and outcome information (e.g. length of stay, intubation, diagnosis).

DATA ANALYSIS

We will follow an intention-to-treat analysis. Descriptive statistics will be used to summarize patient characteristics. Chi-square tests with 95% confidence intervals will be used to examine differences in categorical variables between groups, and two-tailed unpaired t-tests will be used to compare continuous variables. For this pilot study, we have not planned an interim analysis, Data Safety Monitoring Board, or adjudication committee, but these will be developed for the full-scale trial. This trial will be registered with ClinicalTrials.gov.

RISKS

Participation in this study is entirely voluntary. Patients may refuse to participate, refuse to answer any questions, or withdraw from the study at any time with no effect on their future care. Participants do not waive any legal rights by signing the consent form. They will receive a copy of the letter of information should they be willing to consent.

There are no anticipated risks to participating in this study, other than a low possibility of a privacy breach occurring with the data collected during this study. However, the study team will take all necessary precautions to prevent this from happening and will remove any personal identifiers from all data collection forms.

BENEFITS

For participants who are randomized to the Ringer's Lactate Group, there is a possibility that they may benefit from this intervention. The hypothesized benefit from the administration of the IV Ringer's Lactate may include improved faster resolution of DKA than if IV normal saline was administered. However, there is no guarantee that participants will benefit personally from participating in this pilot study.

This study will contribute important knowledge regarding DKA treatment. This pilot study will directly inform us if a full-scale clinical trial evaluating the use of a Ringer's Lactate compared to normal saline as part of DKA care in the ED is possible.

ETHICS AND PRIVACY

We are seeking approval from Western Health Sciences Research Ethics Board. Patient personal health information will be stored confidentially according to standard procedures protected by LHSC firewall. Any paper research records will be stored in a locked cabinet in a secure office at LHSC, and electronic records will be password-protected on Lawson REDCap data storage platform. The data will be viewed only by members of the research team. If the results of this study are published, patient name will not be used and no information that discloses your identity will be released or published. Any identifiable information will be stored separately from the data and will be assigned a unique study code stored separately on a master log. Data will be retained for a period of 15 years after publication in a secure place, after which time it will be destroyed in a secure manner (e.g. shredded or electronically destroyed).
Qualified representatives of the following organizations may look at the study records at the site where these records are held, for quality assurance (to check that the information collected for the study is correct and follows proper laws and guidelines).

Examples include:

- Representatives of Lawson Quality Assurance Education Program
- Representatives of the University of Western Ontario Health Sciences Research Ethics Board that oversees the ethical conduct of this study.

PLANS FOR DISSEMINATION OF FINDINGS

We will present the results from our pilot trial at national and international emergency medicine and diabetes conferences and submit manuscripts including our study protocol and results to peer-reviewed journals for publication. Our overall findings will be communicated via stakeholder organizations (CAEP, NCER, Diabetes Canada, American Diabetes Association), with the goal of changing DKA management guidelines internationally, and will be communicated through medical news/blogs such as EMCases and www.canadiem.org.

CONFLICTS OF INTEREST

This project is funded by the Internal Research Fund (2021-2022) at Lawson Health Research Institute. The study funder is not involved in the design of the study; will not be involved in the collection, analysis and interpretation of data; writing of the manuscript; and will not impose any restrictions regarding publication of the manuscript.