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

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ABSTRACT

Background Current diabetic ketoacidosis (DKA) treatment guidelines recommend using normal saline (NS); however, NS may delay DKA resolution by causing more hyperchloremic metabolic acidosis compared with balanced crystalloids. This study's objective was to determine the feasibility of a future multicentred randomised controlled trial (RCT) comparing intravenous Ringer's lactate (RL) with NS in managing ED patients with DKA.

Methods We conducted a parallel-arm, triple-blind, pilot RCT of adults (≥18 years) with DKA at a Canadian academic tertiary care ED. The primary feasibility outcome was recruitment rate (target ≥41.3% of eligible participants over the 1-year study period); the primary efficacy outcome was time elapsed from ED presentation to DKA resolution. The superiority margin for a clinically significant difference was chosen to be a 40% time reduction to DKA resolution. We also assessed the need to break allocation concealment and loss to follow-up. Patients with clinical suspicion for DKA were screened for inclusion and enrolled patients were randomised 1:1 to receive RL or NS. Patients, clinicians and outcome assessors were blinded to allocation.

Results We enrolled 52 (25 RL, 27 NS) of 60 eligible patients (86.7%), exceeding our target recruitment rate. There were more patients in the NS group with type 1 diabetes, and more patients in the RL group had an admission co-diagnosis in addition to DKA. For the 44 participants with confirmed laboratory evidence of resolution, median (IQR) time to DKA resolution for RL versus NS was 15.7 (10.4–18.8) and 12.7 (7.9–19.2) hours, respectively. There were no cases where blinding was broken, and there was no loss to follow-up.

Conclusions This pilot trial demonstrated our protocol's feasibility by exceeding our target recruitment rate. Our results may be used to inform future multicentre trials to compare the safety and efficacy of RL and NS in managing DKA in the ED.

Trial registration number NCT04926740.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ While current diabetic ketoacidosis (DKA) treatment guidelines recommend using normal saline, concerns about hyperchloremic acidosis have led to suggestions that balanced crystalloids may shorten the time to DKA resolution. However, past studies comparing balanced crystalloids with normal saline in managing DKA have had significant limitations.

WHAT THIS STUDY ADDS

⇒ This pilot trial demonstrated the feasibility of a randomised controlled trial comparing Ringer's lactate versus normal saline in managing DKA in the ED.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ This study's results may be used to inform a future, large, multicentre trial comparing balanced crystalloids and normal saline, which may influence future DKA treatment guidelines.

INTRODUCTION

Diabetic ketoacidosis (DKA) is an acute, life-threatening complication of diabetes which requires treatment with intravenous fluid and insulin to correct hyperglycaemia and reverse acidosis. Current DKA management guidelines recommend normal saline (NS—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 prolong the resolution of DKA in patients who are already in an acidotic state.[4–7]

Alternatives to saline are balanced crystalloids (eg, Ringer's lactate (RL)) which have chloride concentrations similar to human plasma; thus, treatment with balanced crystalloids may lead to faster DKA resolution. There is, however, a lack of high-quality evidence to support choosing balanced crystalloids over NS for adult patients with DKA. A recent systematic review and meta-analysis by Catahay *et al*[8] identified three published randomised trials (Van Zyl *et al*,[9] Self *et al*,[10] Ramanan *et al*[11]) comprising a total of 316 adult patients with DKA. The authors concluded that the use of balanced crystalloids was associated with faster resolution of DKA, but all three studies had significant limitations to their methodology. Van Zyl *et al* was the only trial that used any blinding,[9] but was stopped

prematurely due to slower than expected recruitment and expiry of study consumables. The other two trials were open label, leading to increased risk of bias for participants, personnel and outcome assessors.[10 11] Additionally, the Ramanan *et al* trial was not powered to detect differences in clinical outcomes and only enrolled patients with severe DKA admitted to intensive care units; thus, the results were considered exploratory with limited generalisability to an ED population, most of whom do not have severe DKA. Finally, Self *et al*'s study[10] was a post-hoc subgroup analysis of completed trials (ie, SMART[12] and SALT-ED[13]) and power was not prospectively calculated.

Due to the quality of existing evidence, researchers have called for 'further investigation into the topic of balanced electrolyte solutions vs isotonic saline in adult DKA patients as there are currently very few clinical trials in publication to conclusively make a decision on the verdict'[8] of whether or not they result in faster DKA resolution. Our ultimate goal is to conduct a large multicentre trial examining the benefit and safety of balanced crystalloids versus NS in managing adult patients with DKA. However, a pilot randomised controlled trial (RCT) is necessary to assess the feasibility and obtain vanguard data for this future trial. Therefore, this study's objective was to determine the feasibility of a future full-scale trial comparing intravenous RL versus NS in managing patients with DKA in the ED.

METHODS

Study design and setting

The BRISK-ED Study (Balanced crystalloids (RInger's lactate) versus normal Saline in adults with diabetic Ketoacidosis in the Emergency Department) was a parallel-arm, triple-blind, pilot RCT of adults (≥18 years) presenting to an academic tertiary care ED with DKA over a 1-year period. The study setting was London Health Sciences Centre's (LHSC) Victoria Campus, an academic tertiary care centre with approximately 90 000 ED visits and 130 patients with DKA per year in London, Ontario, Canada. LHSC is the major referral centre for Southwestern Ontario with a catchment population of over 1.5 million people. The study was conducted and reported in accordance with the Consolidated Standards of Reporting Trials statement (online supplemental appendix 1) for pilot feasibility trials,[14] was registered with ClinicalTrials.gov (NCT04926740) and the protocol has been published.[15] The study was overseen by a Data and Safety Monitoring Committee consisting of two ED physicians and a methodologist.

Patient and public involvement

We involved a patient partner in the design and conduct of this trial.

Study population

According to Diabetes Canada guidelines, there are no definitive criteria for diagnosing DKA.[3] Thus, using the criteria employed by Self *et al*[10] and the Diabetes Canada guidelines,[3] we included ED patients ≥18 years with a clinical diagnosis and laboratory values consistent with DKA, including:

- Plasma glucose concentration ≥14 mmol/L.
- Plasma bicarbonate concentration ≤18 mmol/L and/or blood pH ≤7.30.
- Calculated anion gap >10 mmol/L.
- Presence of ketones/β-hydroxybutyrate in serum and/or urine.

Because the diagnosis of DKA requires laboratory confirmation, all patients with a point-of-care blood glucose confirming hyperglycaemia (≥14 mmol/L) were prescreened for enrolment as a 'possible patient with DKA'. During weekday business hours (Monday–Friday, 0800–1800), research assistants (RAs) conducted this task using our ED electronic tracking board before approaching the treating physician to confirm eligibility and clinical suspicion for DKA and obtain consent. Outside of regular business hours, physicians consented and enrolled the patients directly.

We used an integrated model of consent which allows clinicians to obtain informed verbal consent from their own patients or their substitute decision-makers. This approach was approved by our Research Ethics Board as both treatment arms (ie, RL and NS) are considered standard of care at our institution.

Once consented and randomised, intravenous study fluid was administered per the randomisation protocol. If patients were initially enrolled but the physician ultimately confirmed they were not eligible and did *not* meet DKA criteria based on laboratory results (eg, hyperglycaemia without acidosis and/or elevated ketones), they were excluded. We also excluded patients who:

- Were initially seen at another ED and transferred to LHSC for care and/or admission.
- Received >1 L of intravenous fluid prior to enrolment (eg, prehospital by emergency medical services (EMS) or while waiting to be seen) as this may have caused study contamination. One litre of prestudy fluid was the cut-off amount used as an exclusion criterion in the Van Zyl *et al* study.[9]
- Had euglycaemic DKA (generally those on sodium–glucose cotransporter-2 inhibitors).

Interventions

Enrolled patients were randomised in a 1:1 allocation ratio to receive intravenous RL (intervention) or NS (comparator). The rate and volume of study fluid given were at the treating physician's (both ED and inpatient physician, if consulted for admission) discretion. Apart from fluid administered, there were no other changes to the patient's clinical care (ie, patients received other standard DKA treatments which may have included insulin, electrolyte replacement, and/or supportive management). Our hospital's DKA treatment protocol involves hourly point-of-care glucose checks and bloodwork (electrolytes including anion gap and venous blood gas) every 2 hours while receiving insulin infusions.

The randomisation list was prepared by our pharmacy using computer-generated random number tables. Our pharmacy also prepared 8×1 L identically appearing, sequentially numbered, opaque-covered bags of blinded study fluid per kit, and the covering was not removed during the infusion to maintain blinding. This amount was determined based on the study by Self *et al*,[10] where a maximum of 7090 mL of fluid was administered. Patients, the clinical team (including all ED physicians, nurses and any other clinical staff) and outcome assessors (RAs and all investigators) were blinded to allocation group and did not have access to the allocation schedule until after study closure.

Measurements

Study data for each enrolled patient were extracted by trained RAs from the hospital's electronic medical records and entered into Lawson Health Research Institute's Research Electronic Data Capture platform. We collected data on patient characteristics (eg, sex, date of birth), pertinent medical history (eg, comorbidities, medications), arrival ED information (eg, Canadian Triage and Acuity Scale score, arrival vital signs), medical interventions (eg, electrolyte replacement, sodium bicarbonate

administration, medications, other supportive management), laboratory results, and discharge and outcome information (eg, length of stay, endotracheal intubation, intensive care unit admission, discharge diagnoses).

Outcomes

Feasibility outcomes

The primary feasibility outcome was patient recruitment rate defined as the percentage of approached eligible patients successfully recruited over our study period. The target recruitment rate was ≥41.3% of eligible participants (see sample size calculation below). We also assessed the need to break allocation concealment and loss to follow-up (expected to be negligible due to our outcomes being hospital-based and easily determined). To assess for deficiencies in screening and enrolment, we also reviewed daily ED visit logs to identify patients missed by our screening process.

Efficacy outcomes

Our efficacy outcomes were consistent with those used by the previous study by Self *et al*[10]:

- Primary efficacy 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 Crises[1] (plasma glucose <11.1 mmol/L and two of: plasma bicarbonate ≥15 mmol/L, venous pH >7.3 or anion gap ≤12 mmol/L). These criteria were chosen as Diabetes Canada's guidelines lack definitive criteria for DKA resolution, only stating that insulin infusion should continue until ketosis resolves (measured by 'normalisation of plasma anion gap').[3]
- Secondary efficacy outcomes included:
  1. Time to insulin infusion discontinuation (hours).
  2. Intensive care unit admission and length of stay (days).
  3. Total hospital length of stay (days).
  4. In-hospital all-cause mortality.
  5. Hyperkalaemia or hypokalaemia (>6.0 or <3.0 mmol/L) post-ED.
  6. In-hospital acute kidney injury post-ED (stage 2 or greater—defined as serum creatinine increase >200% from baseline or <0.5 mL/kg/hour urine output for <12 hours).
  7. Major adverse kidney events within 30 days, defined as a composite of: (a) death, (b) new renal replacement therapy or (c) final serum creatinine ≥200% baseline at the earliest of hospital discharge or 30 days after ED presentation.

Sample size

The sample size for this pilot study was calculated based on the primary feasibility outcome (ie, participant recruitment rate) using local institutional data and previously published literature. First, we calculated the required sample size for a multicentred RCT with DKA resolution as our primary outcome. 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. Assuming this superiority margin of a 40% minimal clinically important reduction in DKA resolution time and a 10% attrition rate, we would need 516 participants (258 per arm) in a definitive trial, assuming $\alpha=0.05$, power=80% and 1:1 allocation. LHSC treats approximately 130 patients with DKA annually. If at least 104 (80%) patients were approached per year to participate, a minimum of 41.3% (43 participants) would need to be recruited to meet the feasibility target.

According to data from similar trials at our site, we anticipated being able to recruit a minimum of 50% of approached eligible patients. With 104 patients approached, a 90% two-sided CI around the anticipated recruitment rate would have a total width of 17%, that is, a lower limit of 41.5% and an upper limit of 58.5%. Since the lower limit excludes the minimum feasibility target of 41.3%, we would be 90% confident that the future trial is feasible. Thus, our target sample size was 52 patients (26 per arm) over our study period. Online supplemental appendix 2 provides full detail of our sample size calculation.

Data analysis

We followed the intention-to-treat principle for efficacy outcomes. Descriptive statistics including frequencies and proportions were used to summarise patient characteristics. As this was a pilot RCT, statistical significance testing to compare outcomes between groups was not completed in accordance with guidelines for pilot studies, though descriptive information is provided. The Data and Safety Monitoring Committee reviewed blinded data after 50% of our sample size was enrolled. We did not perform interim analyses for this pilot study.

RESULTS

Characteristics of study participants

Over the 1-year study period, we screened 214 patients for eligibility. One hundred eleven were not eligible upon preliminary screening (ie, did not meet DKA criteria or had already received more than 1 L of intravenous fluid prior to screening). Twenty-nine of 103 (28.2%) eligible patients were missed in our screening process (ie, had an ED diagnosis of DKA but not detected on prescreening). The characteristics of missed patients did not differ significantly from enrolled patients.

We approached 74 patients for consent and 8 declined participation. Ultimately, we randomised 66 patients to receive RL (34 patients) or NS (32 patients); however, 14 were subsequently excluded upon further review as they did not meet diagnostic criteria for DKA or received greater than 1 L of fluid before randomisation, leaving 52 included patients in our study. Due to a pharmacy error with respect to the allocation list for one patient, there were 25 patients in the RL group and 27 in the NS group (figure 1).

Median (IQR) age of our study participants was 46 (25–63) years, and 21 of 52 (40.4%) were female. Twenty-six of 52 (50.0%) had a history of type 1 diabetes, 22 of 52 (42.3%) had type 2 diabetes and 4 of 52 (7.7%) had no diabetes history. Data on baseline patient characteristics (demographic information, diabetes type, comorbidities and diabetes medications) are presented in table 1. Table 2 provides ED arrival information, including arrival mode, Canadian Triage and Acuity Scale, vital signs, likely precipitant of DKA and co-diagnoses. Initial and final laboratory values (bicarbonate, anion gap, serum lactate, creatinine, β-hydroxybutyrate, blood gases and serum glucose) and medical interventions (ie, insulin, sodium bicarbonate, intravenous fluid) by patient group are presented in table 3. Trajectory graphs, demonstrating curves of biochemical

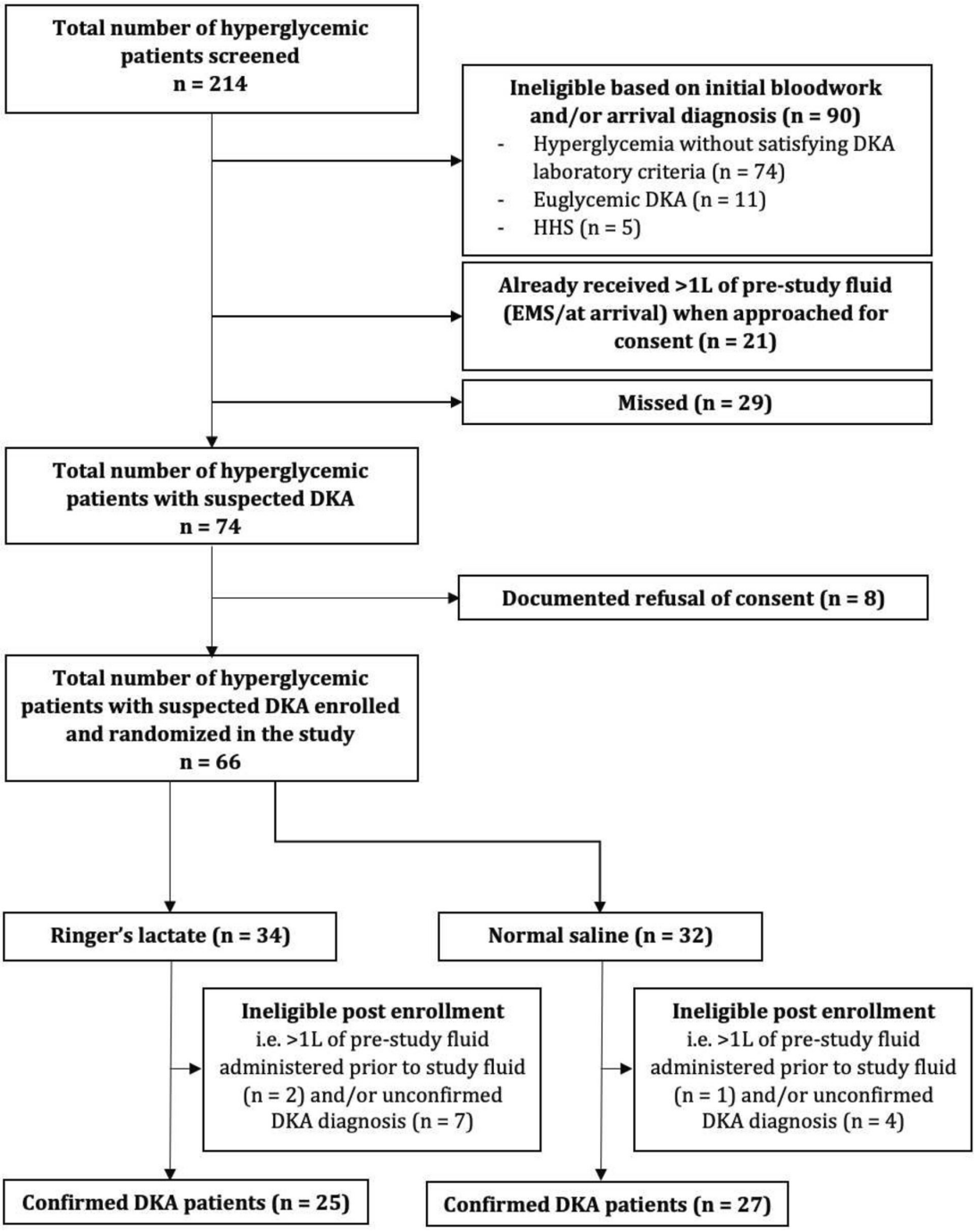

Figure 1 Flow diagram of included patients. DKA, diabetic ketoacidosis; EMS, emergency medical services; HHS, hyperosmolar hyperglycaemic state.

values over time for chloride concentrations, pH, glucose and β-hydroxybutyrate are provided in figure 2.

The study groups were similar, although there were more patients in the NS group with type 1 diabetes (17 of 27 vs 9 of 25 in the RL group), and more patients in the RL group had an admission co-diagnosis in addition to DKA (11 of 25 vs 1 of 27 in the NS group).

Main results

Our participant recruitment rate was 86.7% of approached eligible patients (52 of 60 patients, 95% CI 75.8% to 93.1%), which exceeded the minimum target rate of 41.3%. There were no cases where blinding had to be broken, and no patients were lost to follow-up.

The mean (SD) volume of study fluid administered was 1475±754.8 mL. Although our trial was not powered to demonstrate clinical differences between groups, preliminary efficacy outcomes are presented descriptively in table 4. For the entire cohort, median (IQR) time to insulin infusion discontinuation was 15.9 (5.7–39.2) vs 15.5 (6.7–36.4) hours for RL and NS groups, respectively. The proportion with adverse events (ie, death, intensive care unit admission, intubation, in-hospital acute kidney injury and major adverse kidney events at 30 days) was 28.0% vs 14.8% in the RL group and the NS group, respectively. The RL group had a longer total hospital median length of stay (3.3 vs 1.4 days).

Table 1 Baseline patient characteristics by treatment group

	Ringer's lactate (n=25)	Normal saline (n=27)	Total (n=52)
Demographic information			
Age, years (median (IQR))	47 (33–65)	43 (24–59)	46 (25–63)
Sex, n (%)			
Male	16 (64.0)	15 (55.6)	31 (59.6)
Female	9 (36.0)	12 (44.4)	21 (40.4)
Social history, n (%)			
Tobacco use	8 (32.0)	13 (48.1)	21 (40.4)
Substance use (eg, opioids, cannabis, stimulants)	7 (28.0)	8 (29.6)	15 (28.8)
Alcohol misuse	7 (28.0)	7 (25.9)	14 (26.9)
Medical background			
Diabetes history, n (%)			
Type I	9 (36.0)	17 (63.0)	26 (50.0)
Type II	14 (56.0)	8 (29.6)	22 (42.3)
New diagnosis/no documented history	2 (8.0)	2 (7.4)	4 (7.7)
Comorbidities, n (%)			
Psychiatric illness (eg, depression)	10 (40.0)	11 (40.7)	21 (40.4)
Hypertension	9 (36.0)	12 (44.4)	21 (40.4)
Dyslipidaemia	6 (24.0)	6 (22.2)	12 (23.1)
Chronic kidney disease	6 (24.0)	4 (14.8)	10 (19.2)
Coronary artery disease	2 (8.0)	3 (11.1)	5 (9.6)
Congestive heart failure	3 (12.0)	1 (3.7)	4 (7.7)
Peripheral vascular disease	1 (4.0)	3 (11.1)	4 (7.7)
Cancer	3 (12.0)	0 (0.0)	3 (5.8)
Chronic obstructive pulmonary disease	1 (4.0)	2 (7.4)	3 (5.8)
Stroke or transient ischaemic attack	1 (4.0)	1 (3.7)	2 (3.8)
Dementia	1 (4.0)	1 (3.7)	2 (3.8)
Diabetes medications actively taking at home, n (%)			
Insulin	17 (68.0)	24 (88.9)	41 (78.8)
Oral hypoglycaemics	7 (28.0)	4 (14.8)	11 (21.2)
Metformin	6 (24.0)	3 (11.1)	9 (17.3)
SGLT2 inhibitors	4 (16.0)	1 (3.7)	5 (9.6)
Sitagliptin	2 (8.0)	3 (11.1)	5 (9.6)
Glyburide	1 (4.0)	0 (0.0)	1 (1.9)
Gliclazide	1 (4.0)	0 (0.0)	1 (1.9)
GLP-1 receptor agonists	0 (0.0)	1 (3.7)	1 (1.9)

GLP-1, glucagon-like peptide-1; SGLT2, sodium–glucose cotransporter-2.

Table 2 ED information by treatment group

ED information	Ringer's lactate (n=25)	Normal saline (n=27)	Total (n=52)
Arrival mode, n (%)			
Self	15 (60.0)	11 (40.7)	26 (50.0)
EMS	10 (40.0)	16 (59.3)	26 (50.0)
CTAS, n (%)			
1	3 (12.0)	0 (0.0)	3 (5.8)
2	13 (52.0)	21 (77.8)	34 (65.4)
3	9 (36.0)	6 (22.2)	15 (28.8)
Vital signs (mean±SD)			
Systolic BP (mm Hg)	130.9±24.4	140.8±27.7	136.0±26.4
Diastolic BP (mm Hg)	74.7±18.9	80.5±15.7	77.7±17.4
HR (beats/min)	112.8±26.8	106.6±22.9	109.6±24.8
RR (breaths/min)	19.9±5.7	20.5±5.0	20.2±5.3
Temperature (°C)	36.4±0.9	36.8±0.7	36.6±0.9
O_2 saturation (%)	97.1±2.1	97.2±2.7	97.1±2.4
On O_2 supplement at arrival, n (%)	3 (12.0)	3 (11.1)	6 (11.5)
Blood glucose readings (mean±SD)			
Most recent home glucose (mmol/L)	26.2±16.0	25.0±8.0	25.6±12.0
EMS glucose, if arrival by EMS (mmol/L)	27.2±8.3	22.5±7.5	24.1±7.7
Initial point-of-care glucose (mmol/L)	23.1±6.3	22.8±7.2	22.9±6.7
Likely precipitants of DKA, n (%)			
Poor glycaemic control	10 (40.0)	12 (44.4)	22 (42.3)
Non-adherence to prescribed medication regimen	6 (24.0)	8 (29.6)	14 (26.9)
Unknown cause	6 (24.0)	8 (29.6)	14 (26.9)
New diagnosis	4 (16.0)	1 (3.7)	5 (9.6)
Alcohol related	2 (8.0)	3 (11.1)	5 (9.6)
Infection induced	4 (16.0)	0 (0.0)	4 (7.7)
Co-diagnoses to DKA, n (%)			
Pneumonia	5 (20.0)	0 (0.0)	5 (9.6)
Urinary tract infection	2 (8.0)	0 (0.0)	2 (3.8)
COVID-19	1 (4.0)	0 (0.0)	1 (1.9)
Sarcoidosis	1 (4.0)	0 (0.0)	1 (1.9)
Bowel perforation	1 (4.0)	0 (0.0)	1 (1.9)
Supraventricular tachycardia	1 (4.0)	0 (0.0)	1 (1.9)
Bacteraemia	0 (0.0)	1 (3.7)	1 (1.9)

SD (not included if n≤1).
CTAS, Canadian Triage and Acuity Scale; DKA, diabetic ketoacidosis; EMS, emergency medical services.

Laboratory evidence of DKA resolution was only documented in 44 of 52 (84.6%) participants as some had bloodwork stopped prior to meeting our predefined study criteria for resolution (ie, the clinical teams elected to stop laboratory testing when DKA was improving and had almost resolved but bloodwork results did not quite meet our strict outcome definition). In this group of patients, median (IQR) time to DKA resolution for the RL group was 15.7 (10.4–18.8) and 12.7 (7.9–19.2) hours for the NS group.

DISCUSSION

This blinded pilot RCT demonstrated the recruitment feasibility of a large RCT of RL versus NS in DKA, even when conducted during successive waves of the COVID-19 pandemic. We successfully enrolled patients, exceeded our minimum target recruitment rate and had no breaking of blinding or loss to follow-up. We also successfully used an integrated model of consent, which likely contributed to the high recruitment rate of approached eligible patients. The BRISK-ED protocol and its results can be used to inform a future trial investigating intravenous fluid choice for managing adult patients with DKA in the ED.

Our pilot study highlights several considerations for a future trial design. First, a cluster randomisation design by hospital site, while not essential, would provide several pragmatic advantages, including probable improved recruitment rates to more quickly achieve a desired sample size and reduced time to intervention, which could reduce contamination with non-trial fluids. However, as both the intervention and the primary outcome of interest (ie, time to DKA resolution) occur at the participant

Table 3 Laboratory data and medical interventions by treatment group

Laboratory data	Ringer's lactate initial	Ringer's lactate final	Normal saline initial	Normal saline final	Total initial	Total final
Bicarbonate, mmol/L (mean±SD)	13.7±5.5	22.1±3.8	16.4±6.6	20.0±4.0	15.1±6.0	21.0±4.0
Anion gap, mmol/L (mean±SD)	27.8±9.8	11.9±2.7	23.6±7.6	13.0±3.8	25.5±8.9	12.5±3.3
Serum lactate, mmol/L (median (IQR))	1.9 (1.3–4.7)	1.4 (0.8–2.3)	2.8 (1.8–4.9)	3.2 (2.4–3.6)	2.8 (1.7–4.9)	2.1 (1.0–3.0)
Creatinine, µmol/L (median (IQR))	82.0 (59.0–270.0)	84.0 (50.0–246.0)	95.0 (75.0–159.0)	76.0 (63.0–133.0)	81.5 (64.0–158.3)	76.0 (51.5–141.0)
β-hydroxybutyrate, mmol/L (median (IQR))	5.75 (4.14–8.95)	0.69 (0.66–0.73)	4.07 (2.08–6.96)	0.12 (0.11–0.12)	4.45 (2.40–8.58)	0.38 (0.12–0.66)
Blood gas: pH (mean±SD)	7.22±0.12	7.35±0.06	7.24±0.17	7.34±0.06	7.23±0.14	7.35±0.06
Blood gas: pCO_2 (mean±SD)	35.0±8.6	39.6±6.7	34.7±11.6	39.4±6.3	34.9±10.0	39.5±6.4
Blood gas: pO_2 (mean±SD)	39.1±15.2	47.3±19.2	41.9±15.2	47.4±19.6	40.4±15.0	47.3±19.2
Blood gas: bicarbonate (mean±SD)	17.2±6.8	24.0±5.4	17.6±7.6	21.8±5.6	17.9±7.0	23.0±5.5
Blood gas: lactate (median (IQR))	2.3 (1.7–3.9)	1.8 (1.2–2.2)	2.1 (1.6–3.2)	1.3 (1.1–2.5)	2.2 (1.6–3.5)	1.4 (1.1–2.3)
Serum glucose, mmol/L (mean±SD)	29.0±12.0	11.5±4.0	26.5±9.9	10.1±5.2	27.7±10.9	10.8±4.7

Medical intervention	Ringer's lactate (n=25)	Normal saline (n=27)	Total (n=52)
Prestudy fluid administered, n (%)	4 (16.0)	3 (11.1)	7 (13.5)
Insulin infusion administered, n (%)	23 (92.0)	23 (85.2)	46 (88.5)
Duration of insulin infusion (hours, median (IQR))	15.9 (5.7–39.2)	15.5 (6.7–36.4)	15.7 (6.7–38.2)
Sodium bicarbonate administered, n (%)	4 (16.0)	1 (3.7)	5 (9.6)
Sodium chloride 0.45% administered, n (%)	11 (44.0)	6 (22.2)	17 (32.7)
Total amount of study fluid administered, mL (mean±SD)	1568.0±644.7	1388.9±847.3	1475.0±754.8

SD (not included if n≤1).
pCO_2, partial pressure of carbon dioxide; pO_2, partial pressure of oxygen.

level, individual randomisation may be most appropriate. Furthermore, cluster trials are often associated with recruitment bias and the need for larger samples than would be required in similar, individually randomised trials.[16]

Our study also highlights the importance of robust prescreening, and we believe that participant recruitment could have been more efficient. We did not set an a priori target for missed eligible patients for this pilot study, but 28.2% was higher than anticipated. In a future trial, it would be essential to encourage clinical and research staff to have a low threshold to approach and/or enrol patients with hyperglycaemia before laboratory confirmation of DKA. That being said, the ED is a fast-paced and often uncontrolled environment with unique challenges including overcrowding and high volumes of ill patients which make it difficult for healthcare providers to assist with recruiting patients for research.[17 18] These challenges may have been exacerbated due to the effects of the COVID-19 pandemic on trial conduct in the ED setting.[19] We also note that 21 patients had already received >1 L of prestudy fluid prior to being approached for consent and were thus rendered ineligible. Strategies to mitigate this in future studies include incorporating EMS and paramedics who often give prehospital intravenous fluids into the trial, or using enrolment and intervention strategies that are implemented at the time of initial nursing assessment, especially when there is a prolonged wait time to see the treating ED physician. A waiver of consent, or at least deferred consent in jurisdictions where this is acceptable, could also help mitigate this limitation so that approaching patients for explicit consent would not be necessary.

The amount of study fluid administered to patients in our trial (overall mean=1475 mL) was less than what has been previously reported in trials on this topic (mean of 6798 mL in the balanced crystalloid group vs 6574 mL in the NS group in the Ramanan *et al* study,[11] median of 4267 mL in the balanced crystalloid group vs 4928 mL in the NS group in the Self *et al* study[10]). However, it is important to note that the patients enrolled in those trials were likely more ill than our patient population; the Ramanan *et al* study only included patients with severe DKA admitted to intensive care units,[11] and the Self *et al* study had over 80% of patients admitted to intensive care units. By comparison, we only had one patient in each arm who required admission to the intensive care unit, suggesting that our enrolled patients may have had milder disease and our results may be more representative of a general ED population who may not have severe DKA. Future studies may use a stratified analysis based on severity of DKA to determine for which patients balanced crystalloids versus NS may confer the most benefit and clinical effect.

Limitations

There are several limitations to our study. First, in cases where a patient did not receive the entire bag of study fluid, the treating clinical team had to estimate the amount of fluid administered because the opaque covering limited accurate measurement of any partial bag given, especially if an intravenous pump was not used. Second, there were 17 cases (11 in the RL group, 6 in the NS group) where the treating physicians chose to use 0.45% NS during the DKA recovery phase after the blinded study fluids were administered; this imbalance between groups may have contributed to study contamination in our assessment of time to DKA resolution. In a full-scale trial with a larger sample size, this variable may be better balanced between allocation groups.

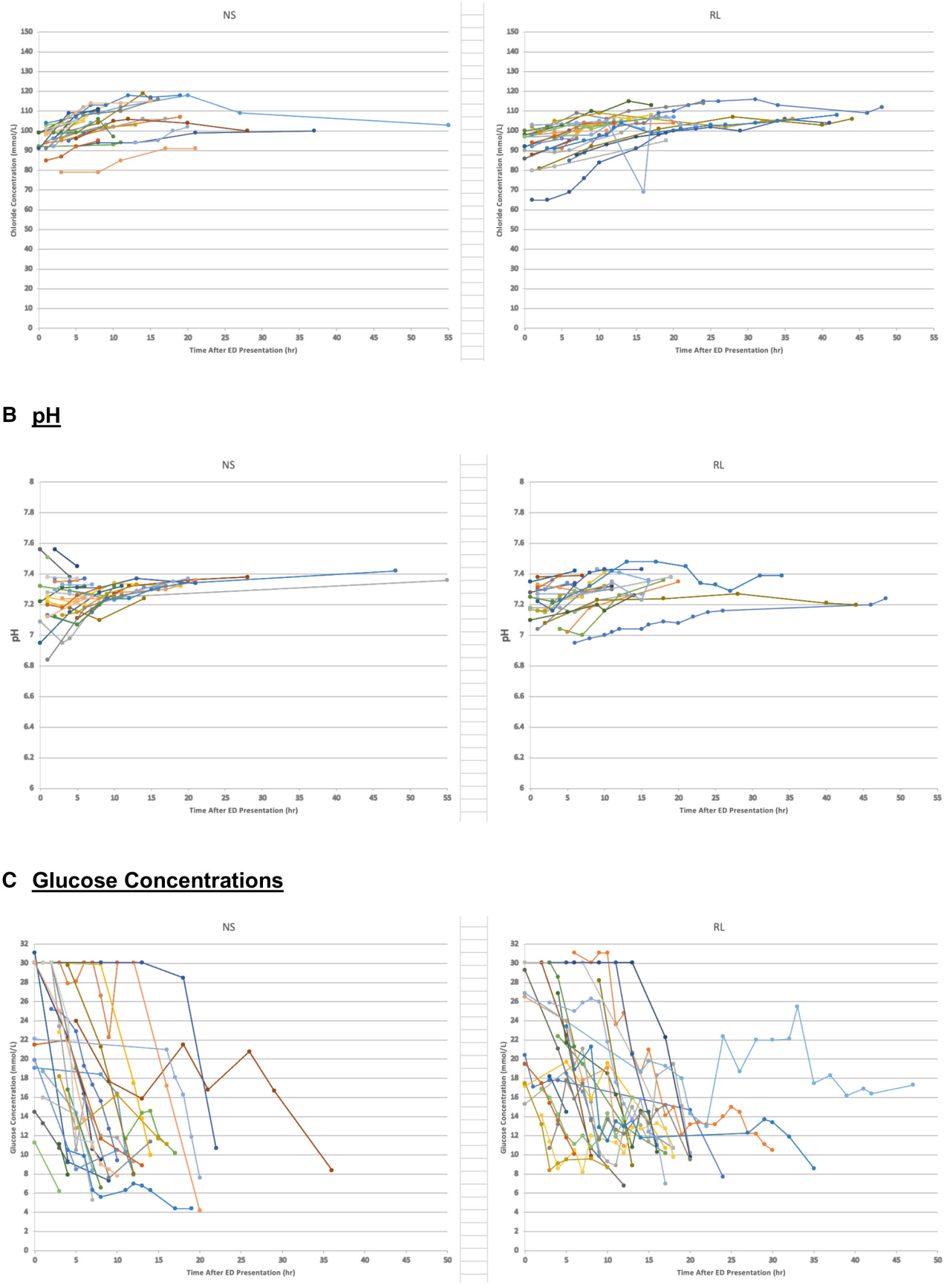

Figure 2 Trajectory graphs for chloride, pH, glucose and β-hydroxybutyrate. (A) chloride concentrations; (B) pH and (C) glucose concentrations. NS, normal saline; RL, Ringer's lactate.

Table 4 Patient outcomes and disposition by treatment group

Patient outcomes	Ringer's lactate (n=25)	Normal saline (n=27)	Total (n=52)
Time to DKA resolution, hours (median (IQR))*	15.7 (10.4–18.8)	12.7 (7.9–19.2)	13.9 (8.8–18.9)
Acute kidney injury in ED/ICU/inpatient unit, n (%)†	4 (16.0)	3 (11.1)	7 (13.5)
Major adverse kidney event within 30 days of ED presentation, n (%)‡	4 (16.0)	2 (7.4)	6 (11.5)
Hyperkalaemia in ED/ICU/inpatient unit, n (%)§	12 (48.0)	5 (18.5)	17 (32.7)
Received treatments for hyperkalaemia: calcium chloride, calcium gluconate, sodium polystyrene sulfonate, furosemide, and/or salbutamol	5 (20.0)	2 (7.4)	7 (13.5)
Hypokalaemia in ED/ICU/inpatient unit, n (%)¶	12 (48.0)	7 (25.9)	19 (36.5)
Received potassium therapy	11 (44.0)	5 (18.5)	16 (30.8)
ED length of stay, hours (mean±SD)	7.6±3.4	8.5±4.7	8.1±4.1
Patients admitted, n (%)	24 (96.0)	18 (66.7)	42 (80.8)
ICU admission, n (%)	1 (4.0)	1 (3.7)	2 (3.8)
ICU length of stay, days (mean±SD)	4	1	2.5±2.1
Total hospital length of stay, days (median (IQR))	3.3 (2.0–6.1)	1.4 (0.3–5.8)	2.2 (0.8–5.7)
Intubation in hospital, n (%)	2 (8.0)	0 (0.0)	2 (3.8)
Seizure in hospital, n (%)	0 (0.0)	0 (0.0)	0 (0.0)

SD (not included if n ≤1).
*Laboratory evidence of DKA resolution was only documented in 44 of 52 (84.6%) participants as some patients had bloodwork stopped prior to meeting our predefined specific study criteria of resolution.
†Stage 2 or greater—defined as serum creatinine increase >200% from baseline or <0.5 mL/kg/hour urine output for <12 hours.
‡Includes: final serum creatinine ≥200% baseline at earliest hospital discharge or 30 days after ED presentation, renal replacement therapy (dialysis), and/or death.
§Serum potassium concentration >5.0 mmol/L at any moment during hospital stay.
¶Serum potassium concentration <3.5 mmol/L at any moment during hospital stay.
DKA, diabetic ketoacidosis; ICU, intensive care unit.

We highlight once again that this pilot trial is not powered to determine clinical differences between groups. This is notable for some secondary outcomes such as total hospital length of stay since the RL group had more admission co-diagnoses which prolonged their length of stay even after their DKA had resolved. Third, it is possible that there may have been selection bias when physicians recruited patients when RAs were unavailable for prescreening. Fourth, as mentioned above, we used strict definitions for both 'DKA' and 'DKA resolution' and were unable to include patients who did not meet our specific study criteria, nor were we able to determine our primary efficacy outcome in cases where laboratory investigations were stopped prematurely, leading to censoring of data for some patients. Finally, this feasibility trial showed a much smaller difference in time to resolution than anticipated and in the opposite direction to our hypothesis. Although this finding may be partially explained by the eight patients who did not demonstrate laboratory-confirmed DKA resolution, these individuals would have to have been very different from the 44 with confirmed DKA resolution to create an effect that is much larger and in the opposite direction. Therefore, a trial with a much larger sample size than we originally anticipated would need to be considered to obtain definitive results to answer this clinical question.

CONCLUSIONS

In summary, although not powered to detect clinical differences between groups, this pilot RCT demonstrated the feasibility of a large RCT as we met our target recruitment rate. Although we met our original recruitment goal, the findings of this study suggest a larger sample size may be needed to detect a clinical difference in any future, full-scale trial. Regardless, our pilot study's protocol and results may be used to inform future, full-scale, multicentre trials to compare the safety and efficacy of balanced crystalloids and NS in managing DKA.

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Contributors JY conceived the study and obtained research funding. JY, KVA, Y-HC, CB, NP, HC and KKC participated in study design. AS acquired data. AS and KVA analysed the data, and all authors assisted with interpretation of the data. JY drafted the manuscript, and all authors contributed substantially to its revision. JY is the guarantor and accepts full responsibility for the work and conduct of the study, had access to the data, and controlled the decision to publish.

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Competing interests Outside of this study, KKC has received a research award sponsored in part by AstraZeneca. She has attended conferences sponsored by Merck. She has received honoraria for delivering certified medical education from Sutherland Global Services Canada ULC, the Canadian Medical and Surgical Knowledge Translation Group and the CPD Network. There are no other conflicts of interest to declare.

Patient and public involvement Patients and/or the public were involved in the design, or conduct, or reporting, or dissemination plans of this research. Refer to the Methods section for further details.

Patient consent for publication Not required.

Ethics approval This study involves human participants and was approved by Western University's Health Science Research Ethics Board (project ID #119430). Participants gave informed consent to participate in the study before taking part.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available upon reasonable request.

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APPENDIX 1: CONSORT Statement Checklist

		Reporting Item	Page Number
Title and Abstract			
Title	#1a	Identification as a randomized trial in the title.	1
Abstract	#1b	Structured summary of trial design, methods, results, and conclusions	3
Introduction			
Background and objectives	#2a	Scientific background and explanation of rationale	5-6
Background and objectives	#2b	Specific objectives or hypothesis	6
Methods			
Trial design	#3a	Description of trial design (such as parallel, factorial) including allocation ratio.	6
Trial design	#3b	Important changes to methods after trial commencement (such as eligibility criteria), with reasons	N/A
Participants	#4a	Eligibility criteria for participants	7
Participants	#4b	Settings and locations where the data were collected	6-7
Interventions	#5	The experimental and control interventions for each group with sufficient details to allow replication, including how and when they were actually administered	8
Outcomes	#6a	Completely defined prespecified primary and secondary outcome measures, including how and when they were assessed	9-10
Outcomes	#6b	Any changes to trial outcomes after the trial commenced, with reasons	N/A
Sample size	#7a	How sample size was determined.	10-11
Sample size	#7b	When applicable, explanation of any interim analyses and stopping guidelines	N/A
Randomization - Sequence generation	#8a	Method used to generate the random allocation sequence.	8
Randomization - Sequence generation	#8b	Type of randomization; details of any restriction (such as blocking and block size)	8
Randomization - Allocation concealment mechanism	#9	Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned	8

Randomization - Implementation	#10	Who generated the allocation sequence, who enrolled participants, and who assigned participants to interventions	8
Blinding	#11a	If done, who was blinded after assignment to interventions (for example, participants, care providers, those assessing outcomes) and how.	9
Blinding	#11b	If relevant, description of the similarity of interventions	8
Statistical methods	#12a	Statistical methods used to compare groups for primary and secondary outcomes	N/A
Statistical methods	#12b	Methods for additional analyses, such as subgroup analyses and adjusted analyses	N/A
Results			
Participant flow diagram (strongly recommended)	#13a	For each group, the numbers of participants who were randomly assigned, received intended treatment, and were analysed for the primary outcome	Figure 1
Participant flow	#13b	For each group, losses and exclusions after randomization, together with reason	Figure 1
Recruitment	#14a	Dates defining the periods of recruitment and follow-up	12
Recruitment	#14b	Why the trial ended or was stopped	N/A
Baseline data	#15	A table showing baseline demographic and clinical characteristics for each group	Table 1
Numbers analysed	#16	For each group, number of participants (denominator) included in each analysis and whether the analysis was by original assigned groups	Figure 1
Outcomes and estimation	#17a	For each primary and secondary outcome, results for each group, and the estimated effect size and its precision (such as 95% confidence interval)	12-13
Outcomes and estimation	#17b	For binary outcomes, presentation of both absolute and relative effect sizes is recommended	12-13
Ancillary analyses	#18	Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing pre-specified from exploratory	N/A
Harms	#19	All important harms or unintended effects in each group (For specific guidance see CONSORT for harms)	12
Discussion			
Limitations	#20	Trial limitations, addressing sources of potential bias, imprecision, and, if relevant, multiplicity of analyses	16-17
Generalisability	#21	Generalisability (external validity, applicability) of the trial findings	14-16

Interpretation	#22	Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence	14-16
Registration	#23	Registration number and name of trial registry	6
Other information			
Interpretation	#22	Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence	14-16
Registration	#23	Registration number and name of trial registry	6
Protocol	#24	Where the full trial protocol can be accessed, if available	7
Funding	#25	Sources of funding and other support (such as supply of drugs), role of funders	1

Appendix 2: Sample Size Calculation

The full-scale multi-centre trial 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(10) 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](12) and the Saline Against Lactated Ringer's or Plasma-Lyte in the Emergency Department [SALT-ED](13_). 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 40% reduction in time to DKA resolution, is 516 participants (258 per group). The sample size was calculated using Wang and Ji's (2020) method 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 prior to protocol development (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 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.