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ORIGINAL

Sodium chloride or Plasmalyte-148 evaluation in severe diabetic ketoacidosis (SCOPE-DKA): a cluster, crossover, randomized, controlled trial

Mahesh Ramanan[1,2,3,4*], Antony Attokaran[5], Lauren Murray[6], Neeraj Bhadange[7], David Stewart[8], Gokulnath Rajendran[9], Raju Pusapati[10], Melissa Petty[1], Peter Garrett[6], Peter Kruger[11], Sandra Peake[12], Laurent Billot[3] and Balasubramanian Venkatesh[3,13] on behalf of the SCOPE-DKA Collaborators and Queensland Critical Care Research Network (QCCRN)

Abstract

Purpose: To determine whether treatment with Plasmalyte-148 (PL) compared to sodium chloride 0.9% (SC) results in faster resolution of diabetic ketoacidosis (DKA) and whether the acetate in PL potentiates ketosis.

Methods: We conducted a cluster, crossover, open-label, randomized, controlled Phase 2 trial at seven hospitals in adults admitted to intensive care unit (ICU) with severe DKA with hospital randomised to PL or SC as fluid therapy. The primary outcome, DKA resolution, was defined as a change in base excess to ≥ -3 mEq/L at 48 h.

Results: Ninety-three patients were enrolled with 90 patients included in the modified-intention-to-treat population (PL $n=48$, SC $n=42$). At 48 h, mean fluid administration was 6798 ± 4850 ml vs 6574 ± 3123 ml, median anion gap 6 mEq/L (IQR 5–7) vs 7 mEq/L (IQR 5–7) and median blood ketones 0.3 mmol/L (IQR 0.1–0.5) vs 0.3 (IQR 0.1–0.5) in the PL and SC groups. DKA resolution at 48 h occurred in 96% (PL) and 86% (SC) of patients; odds ratio 3.93 (95% CI 0.73–21.16, $p=0.111$). At 24 h, DKA resolution occurred in 69% (PL) and 36% (SC) of patients; odds ratio 4.24 (95% CI 1.68–10.72, $p=0.002$). The median ICU and hospital lengths of stay were 49 h (IQR 23–72) vs 55 h (IQR 41–80) and 81 h (IQR 58–137) vs 98 h (IQR 65–195) in the PL and SC groups.

Conclusion: Plasmalyte-148, compared to sodium chloride 0.9%, may lead to faster resolution of metabolic acidosis in patients with DKA without an increase in ketosis. These findings need confirmation in a large, Phase 3 trial.

Keywords: Diabetic ketoacidosis, Diabetes, Critical care, Fluid therapy, Plasmalyte-148, Sodium chloride

*Correspondence: Mahesh.ramanan@health.qld.gov.au
[1] Intensive Care Unit, Caboolture Hospital, McKean Street, Caboolture, QLD 4510, Australia
Full author information is available at the end of the article

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Introduction

Diabetic ketoacidosis (DKA) is a life-threatening complication of diabetes mellitus described in patients with both type 1 and type 2 diabetes [1]. Intravenous fluid replacement and insulin therapy for reversal of ketosis and correction of hyperglycemia remain the cornerstones of therapy. Whilst there is general agreement about the dose and route of insulin administration, the choice of fluid therapy, in both DKA and critical illness in general, is debated [2–5].

Current international guidelines recommend sodium chloride 0.9% (SC) as the replacement fluid of choice [6–8]. Whilst SC is effective in restoring the circulating volume and improving tissue perfusion, its use in large volumes is associated with hyperchloremia [9], and in DKA is associated with non-anion gap metabolic acidosis [10–13] and prolonged lengths of stay in intensive care unit (ICU) [14] and hospital [15, 16].

Plasmalyte-148 (PL) is a buffered salt solution that contains lower chloride concentrations than SC and acetate and gluconate as additional anions. It has been evaluated in two small randomized trials, one each in pediatric [17] and adult patients [18] with DKA. The pediatric trial demonstrated no differences between the PL and SC groups in the development of acute kidney injury (the primary outcome) or other clinical outcomes. The adult trial demonstrated faster resolution of acidosis in the PL group. A secondary analysis of two other cluster randomized trials showed faster resolution of DKA with the use of balanced crystalloids (including PL and compound sodium lactate) compared to SC [19].

Whilst PL may be effective in DKA, its safety profile in patients with severe DKA has not been formally assessed. PL contains acetate at a concentration of 27 mmol/L [20]. Acetate is a precursor for acetoacetate, one of the ketone bodies. Acetoacetate is converted to beta-hydroxybutyrate, the predominant ketone body in DKA [21, 22]. In dogs, acetate infusions have been accompanied by increases in acetoacetate concentrations [23]. Liver mitochondrial fractions in rats convert acetate to acetoacetate [24]. In humans, there is evidence that acetate may contribute to ketogenesis, particularly in the setting of hemodialysis [25, 26]. Whether a similar metabolic step of clinically significant proportions occurs in patients with DKA has never been evaluated.

We designed the 'Sodium chloride or Plasmalyte-148 evaluation in severe diabetic ketoacidosis' (SCOPE-DKA) trial to test the hypothesis that in critically ill patients with severe DKA, PL would result in faster resolution of DKA than SC and will not increase ketone generation.

Take-home message

Plasmalyte-148 compared to sodium chloride 0.9%, as intravenous fluid therapy, may result in faster resolution of metabolic acidosis in adult patients with severe diabetic ketoacidosis

Plasmalyte-148, when used as intravenous fluid therapy for patients with diabetic ketoacidosis, does not result in an increase in ketosis

Methods

Study design and participants

The SCOPE-DKA trial was prospectively registered with the Australia New Zealand Clinical Trials Registry (ACTRN12618001622291) and reported here according to the CONSORT extension for cluster trials guidelines [27]. Ethics approval was granted by the Royal Brisbane and Women's Hospital Human Research Ethics Committee (HREC/2018/QRBW/43868) for this trial to be conducted at all participating sites with a full consent waiver.

SCOPE-DKA was a cluster, crossover, open-label, randomized, controlled trial comparing the use of PL and SC for patients with severe DKA conducted in seven Australian intensive care units (ICU) over a 13-months period including two 6-months intervention periods and a 1-month washout period in the middle. Each ICU was a single cluster, with all patients admitted with DKA to that ICU during the intervention periods potentially eligible for inclusion in the trial. After the first 6-months intervention period, there was a 1-month washout period during which patients were not recruited into the trial. As this trial was a cluster-randomized, crossover, design, where recruitment was conducted over a fixed time period, there was no pre-determined sample size. Trial conduct was overseen by an independent data safety monitoring committee (DSMC) who performed a safety review during the washout period on data from the first intervention period. Following DSMC's advice to continue recruitment, the sites then crossed over to the other fluid for the second intervention period.

All patients 16 years of age and over who presented to the emergency department (ED) or ICU at a participating site during either intervention period with severe DKA were eligible for recruitment. Severe DKA was defined as arterial pH $\leq$ 7.25 (or serum bicarbonate $\leq$ 15 mmol/L) and blood glucose $\geq$ 14 mmol/L and requirement for ICU admission in the judgement of the treating clinician [28]. Based on Australian data [29], which showed that the temporal rise in DKA ICU admissions was predominately in rural and metropolitan hospitals (as opposed to tertiary and private hospitals), all sites that were invited to participate in SCOPE-DKA were rural or metropolitan hospitals.

Patients were excluded if they were under 16 years of age, had previously been included in this trial, had a contraindication to either fluid or had a suspected diagnosis of the hyperosmotic hyperglycemic non-ketotic syndrome.

Randomisation

Participating sites were allocated using randomly generated computer tables in a 1:1 ratio to PL or SC for the first intervention period. All sites crossed over to the alternate allocation for the second intervention period. Allocation for the first intervention period was concealed from the sites until 1 week prior to commencement.

Procedures

All included patients received open-label PL or SC, depending on the fluid assigned to the site for the relevant intervention period, as part of their DKA therapy. The volume and rate of administration of fluids were guided by clinical and biochemical endpoints determined by the treating clinician. All other aspects of DKA therapy, such as insulin and electrolyte replacement, were managed as per local protocols. The only aspect of management stipulated by this trial was the fluid type. Study treatment commenced as soon as practical once the diagnosis was made and eligibility criteria were confirmed by ED staff. The intervention continued for 48 h from ICU admission. If patients were discharged from ICU within 48 h, fluid choice after ICU discharge was determined by the treating clinician on the wards. The study fluid was used for all resuscitation and intravenous maintenance purposes. Diluents for infusions, electrolyte replacement, dextrose-containing solutions for glucose control, albumin, and bicarbonate-containing fluids were able be administered for specific indications as per local protocols. The frequency of blood testing was at the discretion of the treating clinician.

Outcomes

The primary outcome was a change in base excess to ≥ -3 mEq/L at 48 h post-ICU admission. Sensitivity analyses for the primary outcome were: (1) change in base excess to ≥ -3 mEq/L at 24 h post-ICU admission and (2) fulfilment of American Diabetes Association (ADA) criteria for DKA resolution at 24 h post-ICU admission i.e., plasma glucose < 11.1 mmol/L and two of the following: plasma bicarbonate $\geq$ 15 mmol/L, venous pH > 7.3 and anion gap $\leq$ 12 mEq/L.

Secondary outcomes were ICU and hospital mortality and lengths of stay, the proportion of patients receiving organ support (invasive and non-invasive ventilation, acute renal replacement therapy) and cumulative urine output and fluid balance at 24, 48, and 72 h post-ICU admission. Other biochemical outcomes included serum sodium, potassium and chloride concentrations, pH, pCO_2, pO_2, base excess, anion gap, blood glucose (BGL) and ketone concentrations at 6, 12, 18, 24, 36, 48, and 72 h post-ICU admission or at the timepoint closest to these times.

Safety data included the proportion of patients with severe hypokalemia (serum potassium < 3 mmol/L), hypoglycemia (plasma glucose < 3.8 mmol/L), hypophosphatemia (serum phosphate < 0.7 mmol/L), hypocalcemia (ionized calcium < 1 mmol/L) and persistent ketosis (blood ketone concentration > 1.5 mmol/L) at 24 h post-ICU admission or any adverse events deemed by the treating clinician to be related to the administered study fluid.

Compliance with fluid allocation was defined as the proportion of the total fluid received by each patient that was consistent with the allocation. For example, if a patient in the PL group received 5000 ml of fluid overall, and 4000 ml of this was PL, compliance would be 80%. Compliance was assessed overall, as well as in the ED and ICU separately.

Biochemical analyses, including electrolytes and acid–base values, were measured using point-of-care blood gas analysers. Ketone concentrations were measured on capillary blood samples using point-of-care blood ketone analysers. These devices measure beta-hydroxybutyrate. All measurements were performed at the individual sites using locally available devices.

Statistical analysis

All outcomes were analyzed at an individual patient level on a modified intention-to-treat basis (i.e., patients with complete outcome data for the primary outcome) according to the fluid allocation, regardless of the type of fluid received.

Continuous variables were reported as the median and interquartile range (IQR) or mean and standard deviation (SD). Categorical variables were reported as frequencies and proportions. To adjust for cluster-level correlation, logistic mixed models were used with group allocation as a fixed effect and site as a random effect with patients nested within sites. Given the small expected sample size, we did not add a random cluster-period effect, thus assuming constant correlations within a site regardless of the period. Differences between groups were reported as odds ratio (OR) for categorical outcomes and mean difference for continuous outcomes, both with 95% confidence intervals (CI). Repeated measures mixed-effects models were constructed to assess the changes in the biochemical variables (pH, base excess, anion gap, bicarbonate, sodium, chloride, glucose and ketones) over time between the two groups. *P*-values have been reported for

the primary outcome but without a threshold for statistical significance given the trial was not powered to specifically investigate a between-group difference in the primary outcome.

All analyses were performed in Stata 13.0 (StataCorp, College Station, TX-USA).

Funding source

There was no specific funding source for SCOPE-DKA. This trial was performed using in-kind support from the participating sites.

Results

Patients

From September 2019 to September 2020, we enrolled 93 patients at 7 sites: 50 (54%) into the PL group and 43 (46%) into the SC group. Details of the recruitment are presented in Fig. 1. Individual sites recruited between 2 and 24 patients. One site commenced recruitment but was unable to continue recruitment for the entire duration of the trial due to unanticipated changes to local staffing and resourcing. The two patients recruited at this site were lost to follow-up and did not have any treatment or outcome data, therefore, they were not included in the analyses. There was one additional patient with missing data for the primary outcome, leaving a final modified-intention-to-treat-analysis cohort of 90 patients: 48 (53%) in the PL group and 42 (47%) in the SC group.

Patient baseline characteristics are presented in Table 1. Briefly, the age and sex distributions, body mass index and clinical observations at ED presentation were similar between the two groups. There were more patients with Type 1 diabetes (83% versus 67%), higher initial anion gap (32 mEq/L, IQR 24–35 versus 28 mEq/L, IQR 25–32) and higher initial blood ketone concentrations (6.2 mmol/L, IQR 5.6–7.7 versus 5.4 mmol/L, IQR 4.9–6.7) in the PL versus SC group.

Fluid types and volumes administered

The mean volume of fluid administered up to 48 h post-ICU admission in the PL and SC groups were 6798 ml (SD 4850) and 6574 ml (SD 3123) respectively (Supplemental Table S1).

Compliance with treatment allocation was 66% (IQR 38–85%) in the PL group and 100% (IQR 75–100%) in the SC group (Supplemental Table S1). There were seven patients (15%) in the PL group who received PL for ≥ 95% of their administered fluids compared to 23 patients (55%) in the SC group who received SC for ≥ 95% of their administered fluids.

Compliance with PL treatment allocation was greater in the ICU; 76% (IQR 41–95%) versus 50% (IQR 0–99%) in the ED.

Primary outcome

The primary outcome (base excess ≥ −3 mEq/L at 48 h post-ICU admission) was attained by 46 patients (96%) in the PL group and 36 patients (86%) in the SC group. After adjustment for site-level random effects in the mixed effects logistic regression model, the OR for attaining the primary outcome was 3.93 (95% CI 0.73–21.16, $p = 0.111$). In a post hoc analysis using repeated measures mixed-effects modelling, base excess was significantly higher in the PL group at 24 h (+3.6 mEq/L, 95% CI 1.1–6.2, $p = 0.005$) and 48 h (+3.5 mEq/L, 95% CI 0.4–6.7, $p = 0.026$) (Supplemental Table S2). In the pre-specified sensitivity analyses (Table 2), the adjusted OR was 4.24 (95% CI 1.68–10.72, $p = 0.002$) when base excess ≥ −3 mEq/L at 24 h post-ICU admission was used to define DKA resolution and 1.47 (95% CI 0.61–3.52, $p = 0.390$) using the ADA criteria.

Two additional post-hoc sensitivity analyses were performed with the addition of base excess at presentation and diabetes type as fixed effects given the baseline imbalance between the two groups for these two variables. Upon addition of base excess at presentation, the OR for the primary outcome was 4.15 (95% CI 0.77–22.34, $p = 0.097$). Upon addition of diabetes type, the OR was 3.15 (95% CI 0.52–18.96, $p = 0.211$). When both were added, the OR was 2.95 (95% CI 0.5–17.54, $p = 0.234$).

The median blood ketone concentration at 48 h was 0.3 mmol/L (IQR 0.1–0.5) and 0.3 mmol/L (IQR 0.1–0.5) in the PL and SC groups. The median anion gap at 48 h was 6 mEq/L (IQR 5–7) and 7 mEq/L (IQR 5–7) in the PL and SC groups, respectively. The median serum chloride concentrations at 48 h were 106.5 mmol/L (IQR 103–110) and 108 (IQR 104–113) in the PL and NS groups. In the repeated measures mixed-effects model, the PL group had significantly lower serum chloride concentrations at 24 h (−3.5 mmol/L, 95% CI −6.4 to −0.5, $p = 0.021$) and similar serum chloride concentrations at 48 h (−2.9 mmol/L, 95% CI −6.5 to 0.6, $p = 0.106$). The changes in blood ketone concentrations, anion gap and other biochemical results over the first 48 h are presented graphically in Figs. 2 and 3.

Insulin and electrolytes administered in 48 h

The median insulin infusion dose administered to patients in both groups was similar- 0.08 units/kg/h (IQR 0.06–0.12) in the PL group and 0.08 units/kg/h (IQR 0.05–0.12) in the SC group. The PL group received a median of 78 mmol (IQR 39–130) intravenous potassium replacement and the SC group received a median of 116 mmol (IQR 40–211). The corresponding values for phosphate replacement were 20 mmol (0–32) and 13 mmol (IQR 0–27).

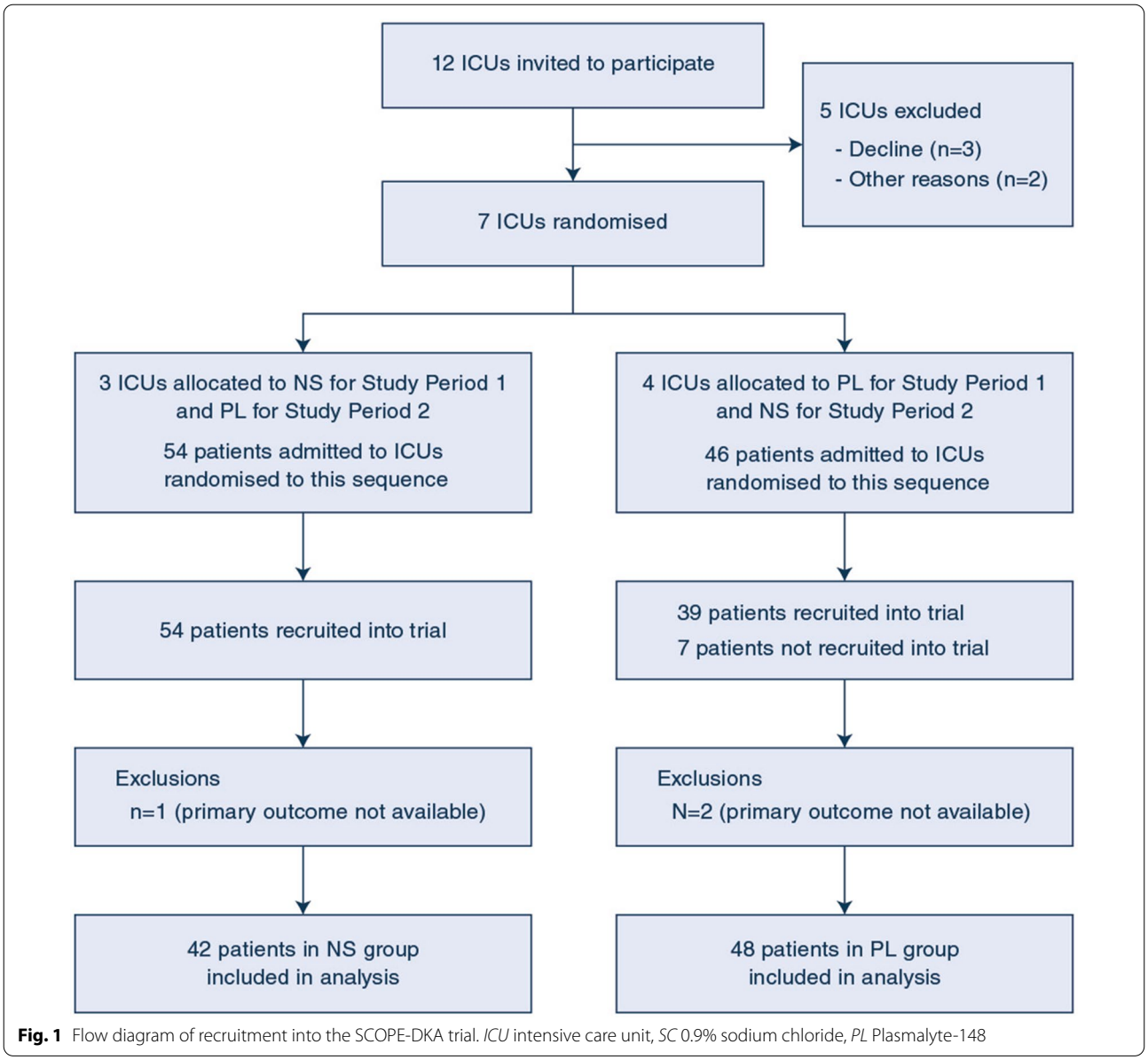

Fig. 1 Flow diagram of recruitment into the SCOPE-DKA trial. *ICU* intensive care unit, *SC* 0.9% sodium chloride, *PL* Plasmalyte-148

Clinical outcomes

The median ICU lengths of stay were 49 h (IQR 23–72) and 55 h (IQR 41–80) in the PL and SC groups. Hospital length of stay also tended to be shorter in the PL group; 81 h (IQR 58–137) versus 98 h (IQR 65–195) in the SC group. ICU readmission rates were 4% (2 of 48) in the PL group and 2% (1 of 42) in the SC group. Kaplan–Meier curves of time to ICU and hospital discharge are presented Supplemental Figures S1 and S2. One death occurred in the SC group in a patient who died from rhinocerebral mucormycosis.

Adverse events

Adverse events were similar between groups (Supplemental Table S3). Hypoglycemia occurred in 9 (19%) and 11 (26%) patients in the PL and SC groups, respectively. Hypophosphatemia occurred in 33 (69%) and 34 (81%) patients and persistent ketosis in 5 (10%) and 5 (12%) patients, respectively. Severe hypokalaemia occurred in 5 (10%) patients in the PL group and 7 (17%) in the SC group.

Missing data

Missing data ranged from 0 to 5% for the considered variables in the intention-to-treat analysis sample of 90 patients (Supplemental Table S4).

Table 1 Patient characteristics at ED admission

Characteristic	PL $n=48$	SC $n=42$
Age, years	36.7 (23.7–51.2)	38.1 (24.4–53.2)
Female sex	26 (54%)	24 (57%)
Diabetes type		
Type 1	40 (83%)	28 (67%)
Type 2	6 (13%)	9 (21%)
Newly diagnosed (not yet typed)	2 (4%)	5 (12%)
Previous DKA admissions	29 (60%)	25 (60%)
Body-mass index, kg/m^2	22.2 (19.1–26)	23.1 (20.6–26.7)
Clinical findings at presentation		
Heart rate, beats per minute	115 (100–125)	110 (92–125)
Respiratory rate, breaths per minute	26 (21–30)	22 (20–26)
Systolic blood pressure, mm Hg	124 (109–150)	118 (103–139)
Glasgow coma score	15 (13–15)	15 (13–15)
Laboratory values at presentation		
pH	6.99 (6.86–7.07)	7.02 (6.89–7.08)
Base excess, mEq/L		
≥ -8	0 (0%)	0 (0%)
-8.1 to -16.0	3 (6%)	4 (10%)
-16.1 to -24.0	17 (35%)	19 (45%)
≤ -24.1	28 (58%)	19 (45%)
Median base excess, mEq/L	-25.2 (-21.2 to -28.7)	-23.7 (-21.2 to -28.7)
Glucose, mmol/L	31.4 (19.9–41.6)	30.2 (23.8–44.7)
Sodium, mmol/L	136 (132–140)	135 (128–138)
Chloride, mmol/L	100 (95–106)	100 (94–105)
Blood ketones, mmol/L	6.2 (5.6–7.7)	5.4 (4.9–6.7)
Anion gap, mEq/L	32 (24–35)	28 (25–32)

Data are *n* (%) or median (interquartile range)

ED emergency department, *PL* Plasmalyte-148, *SC* 0.9% sodium chloride, *DKA* diabetic ketoacidosis

Table 2 Resolution of diabetic ketoacidosis

Outcome	PL $n=48$	SC $n=42$	Odds ratio (PL vs NS)	95% confidence interval	*p* values*
Primary outcome					
Base excess > -3.0 mEq/L at 48 h	46 (96%)	36 (86%)	3.93	0.73–21.16	0.111
Pre-specified sensitivity analyses					
Base excess > -3.0 mEq/L at 24 h	33 (69%)	15 (36%)	4.24	1.68–10.72	0.002
ADA criteria for DKA resolution at 24 h	29 (60%)	22 (52%)	1.47	0.61–3.52	0.390
Post-hoc sensitivity analyses					
Addition of base excess at presentation	46 (96%)	36 (86%)	4.15	0.77–22.34	0.097
Addition of diabetes type	46 (96%)	36 (86%)	3.15	0.52–18.96	0.211
Addition of both base excess at presentation and diabetes type	46 (96%)	36 (86%)	2.95	0.50–17.54	0.234

Data in columns 'PL' and NS' are *n* (%)

PL Plasmalyte-148, *SC* 0.9% sodium chloride, *ADA* American Diabetes Association, *DKA* diabetic ketoacidosis

**p* values: All results were generated from a mixed effects logistic regression model with treatment allocation (PL versus SC) as a fixed effect and site as a random effect. For the post-hoc sensitivity analyses, the specified fixed effect/s were added. The odds ratio for resolution of diabetic ketoacidosis in PL group compared to the SC group are presented, therefore, an odds ratio greater than 1 indicates an increase in resolution with PL treatment

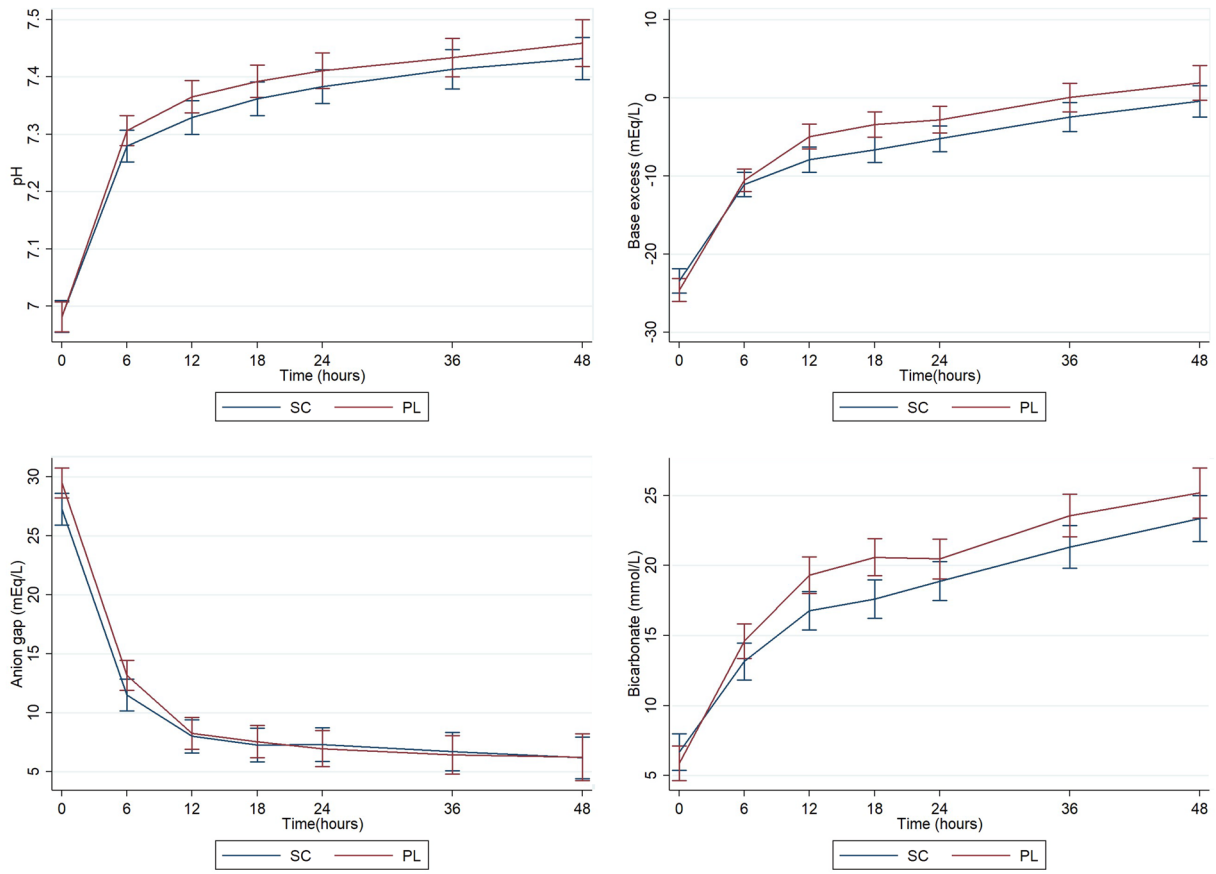

Fig. 2 Changes in pH, base excess, anion and bicarbonate during the first 48 h in the intensive care unit are shown here with 95% confidence intervals. Estimates presented here were generated using mixed-effects models to account for repeated measures. *SC* 0.9% sodium chloride, *PL* Plasmalyte-148

Discussion

Key findings

The SCOPE-DKA Phase 2 trial has demonstrated that treatment of patients with severe DKA with PL compared to SC may result in faster resolution of metabolic acidosis, accompanied by lower serum chloride concentrations, and without any increase in ketone generation. Clinical and safety outcomes were similar between the two groups.

Our trial evaluated the effect of two different crystalloid fluids on the rate of resolution of acidosis in patients with severe DKA. We adopted a cluster-crossover design because of the associated pragmatic benefits; including reduced setup and education costs, easier delivery of the trial intervention as a fluid choice was incorporated into hospital DKA guidelines at each site and higher recruitment rates due to consent waiver. We chose base excess as a primary outcome and specifically targeted a population of patients with severe DKA who are likely to be dehydrated and have high requirements for fluids. The trial was successful in enrolling the intended population. A high proportion of eligible patients received the trial intervention as planned, and few enrolled patients were lost to follow-up.

Our trial differs from previously published data in several respects. Previous RCTs investigating fluids in DKA have been small and only one has evaluated PL in adult patients. Results of our Phase 2 trial will inform the conduct of a large, well-powered, confirmatory trial in the future. Our results are in accord with a recent report of a subgroup analysis of adults with DKA in 2 large cluster randomized trials evaluating balanced crystalloids (both compound sodium lactate and PL) versus SC in ED and ICU patients [19]. Plasma ketone concentrations were not reported in that study.

Safety concerns

One of the significant concerns with the use of PL in DKA is the potential for acetate anions contained in PL to be converted to acetoacetate, one of the "ketone bodies" and

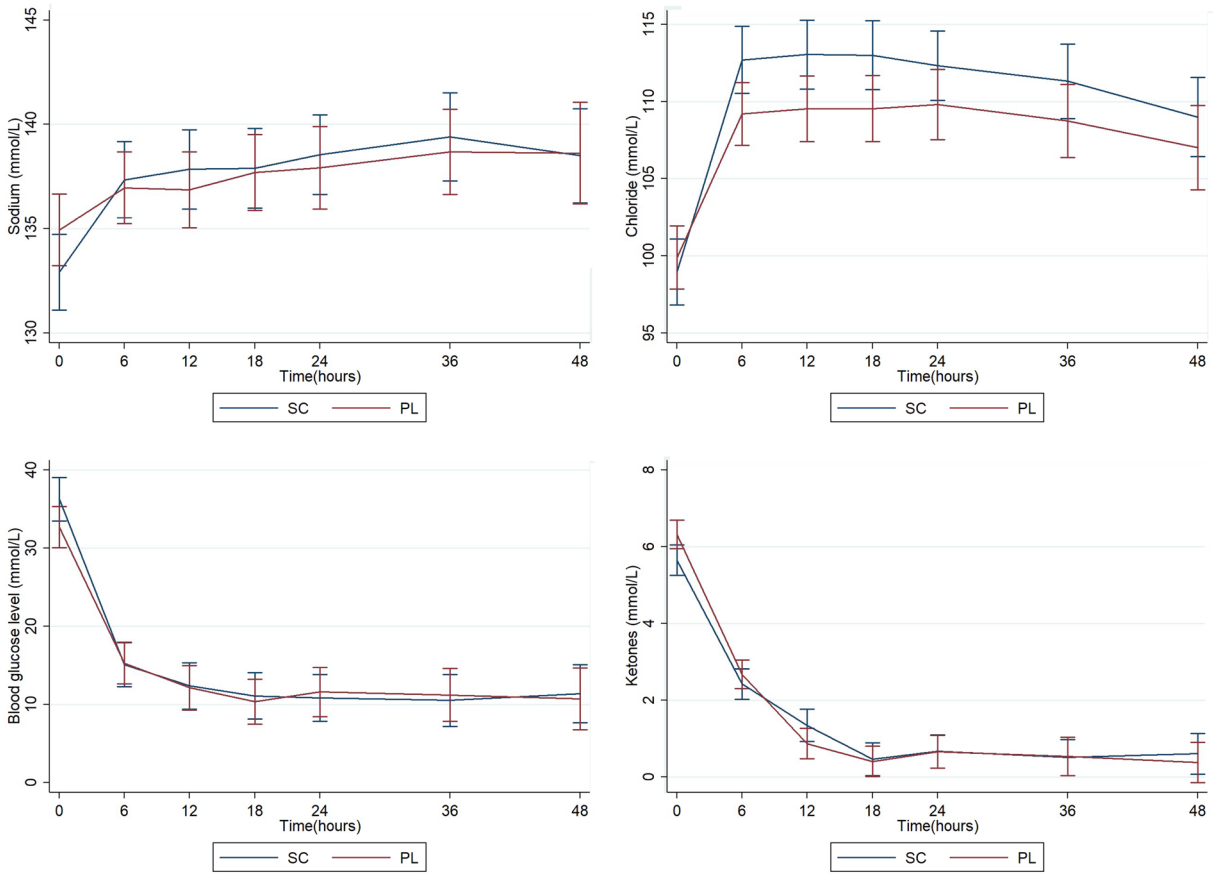

Fig. 3 Changes in sodium, chloride, blood glucose level and ketones during the first 48 h in the intensive care unit are shown here with 95% confidence intervals. Estimates presented here were generated using mixed-effects models to account for repeated measures. *SC* 0.9% sodium chloride, *PL* Plasmalyte-148

potentiate the ketosis. We did not observe an increase in ketosis, in fact, the rates were 14% at 24 h into the ICU admission in both groups. Resolution of DKA using multiple different definitions tended to be faster in the PL group, thus supporting our hypothesis that acetate in PL does not contribute to excess ketone generation in DKA. This is consistent with the finding that acetate infusions (4 mmol/kg over 1 h) in healthy volunteers resulted in only a small rise in plasma acetate concentrations and a metabolic alkalosis with acetate having a rapid plasma clearance of 2.31 L/min [30]. Comparatively, 1 L of PL-148 contains 27 mmol/L of acetate which is equivalent to 0.39 mmol/kg in a 70 kg individual.

The frequency of some adverse events, such as hypoglycemia and hypophosphatemia were also lower in the PL group.

Limitations

Our trial had limitations. As a Phase 2 trial not powered to detect differences in clinical outcomes, the clinical results can only be considered exploratory. While there was a separation between the groups in terms of the fluids administered, adherence to allocated fluids was not high in the PL group. There were substantial volumes of SC used, although if it influenced the clinical outcomes, it would tend to bias the results towards the null (Type-2 error) rather than leading to an erroneous conclusion of superiority (Type-1 error) for PL. As this trial allowed for usual local practices for drug dilution, often done using SC, it is likely that some of the non-compliance in the PL group can be explained by this. Additionally, compliance was better overall in ICU compared to ED, which may reflect greater familiarity with PL use amongst intensive care staff and better education of ICU compared to ED staff with regards to trial procedures.

Conclusion

In conclusion, for patients with severe DKA, treatment with PL compared to SC may result in faster resolution of metabolic acidosis. The use of PL was not associated with an increase in ketone generation.

Supplementary Information
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Author details
[1] Intensive Care Unit, Caboolture Hospital, McKean Street, Caboolture, QLD 4510, Australia. [2] Adult Intensive Care Services, The Prince Charles Hospital, Rode Road, Chermside, QLD 4032, Australia. [3] The George Institute for Global Health, University of New South Wales, Level 5/1 King Street, Newtown, NSW 2042, Australia. [4] School of Medicine, University of Queensland, Sir Fred Schonell Drive, St Lucia, QLD 4072, Australia. [5] Intensive Care Unit, Rockhampton Hospital, Canning Street, Rockhampton, QLD 4700, Australia. [6] Intensive Care Unit, Sunshine Coast University Hospital, Doherty Street, Birtinya, QLD 4575, Australia. [7] Intensive Care Unit, Ipswich Hospital, Chelmsford Avenue, Ipswich, QLD 4305, Australia. [8] Intensive Care Unit, Queen Elizabeth-2 Jubilee Hospital, Kessels Road, Coopers Plains, QLD 4108, Australia. [9] Intensive Care Unit, Mackay Base Hospital, Bridge Road, Mackay, QLD 4741, Australia. [10] Intensive Care Unit, Hervey Bay Hospital, Urraween Road, Pialba, QLD 4655, Australia. [11] Intensive Care Unit, Princess Alexandra Hospital, Ipswich Road, Woolloongabba, QLD 4102, Australia. [12] Department of Intensive Care Medicine, The Queen Elizabeth Hospital, Woodville Road, Woodville South, South Australia 5011, Australia. [13] Intensive Care Unit, Wesley and Princess Alexandra Hospitals, Woolloongabba, QLD, Australia.

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SCOPE-DKA Collaborators and Sites: Mark Scott: Staff Specialist, Emergency Department, Caboolture Hospital, Brisbane, Queensland, Australia; Stacey Watts: Research Coordinator, Emergency Department, Caboolture Hospital and Kilcoy and Woodford Correctional Health, Brisbane, Queensland, Australia; Timothy Harding: Staff Specialist, Emergency Department, Ipswich Hospital, Ipswich, Queensland, Australia; Senior Lecturer, School of Medicine, University of Queensland, Brisbane, Queensland, Australia; Steven Tyler: Clinical and Research Nurse, Intensive Care Unit, Ipswich Hospital, Ipswich, Queensland, Australia; Bauke Hovinga: Assistant Clinical Director, Department Emergency Medicine, Mackay Base Hospital, Mackay, Queensland. Australia; Tracy Joy Hess: Clinical Trials Nurse, Mackay Institution of Research and Innovation, Mackay, Queensland. Australia; School-Based Immunisation Nurse (Endorsed), Queensland Health; Rajbir Sing Sandha: Staff Specialist- ED, Rockhampton Hospital, Canning Street, The Range, QLD , Australia 4700; David Austin: Director—Intensive Care Services, Central Queensland Health Service, Rockhampton, QLD, Australia 4700; Syed Giasuddin Khadri: Clinical Director—Emergency Department Rockhampton Hospital, Canning Street, The Range, QLD, Australia 4700; Salomon Jacobus Poggenpoel: Deputy Director ICU, Rockhampton Hospital, Canning Street, The Range, QLD, Australia 4700; Helen Miles: Staff Specialist, Intensive Care Unit, Rockhampton Hospital, Canning Street, The Range, QLD , Australia 4700; Associate Lecturer, University of Queensland; Jane Brailsford: Intensive Care Unit, Sunshine Coast University Hospital, Birtinya, Australia; Teena Maguire: Intensive Care Unit, Sunshine Coast University Hospital, Birtinya, Australia; Kym Roberts: Department of Emergency Medicine, Sunshine Coast University Hospital, Birtinya, Australia; Ogilvie Thom: Department of Emergency Medicine, Sunshine Coast University Hospital; Isuru Seneviratne: Staff Specialist, Intensive Care Unit, Queen Elizabeth-2 Jubilee Hospital, Brisbane, Queensland, Australia; David Stewart: Staff Specialist, Intensive Care Unit, Queen Elizabeth-2 Jubilee Hospital, Brisbane, Queensland, Australia.

Data Safety Monitoring Committee: Anthony Russell FRACP Director of Endocrinology, Princess Alexandra Hospital, Brisbane, Queensland, Australia Associate Professor, School of Medicine, University of Queensland, Brisbane, Queensland, Australia. Michael D'Emden FRACP Director of Endocrinology, Royal Brisbane and Women's Hospital, Brisbane, Queensland, Australia. Kunwarjit Sangla FRACP Staff Specialist, Endocrinology, Rural Hospital Services Group, Queensland Health, Queensland, Australia.

Queensland Critical Care Research Network (QCCRN): The QCCRN was formed in June 2017 with a mission *"to foster a state-wide collaborative approach to critical care research with the goals of increasing research capacity in Queensland's Intensive Care Units and support high quality research output from local investigators with a focus on improving patient outcomes".* QCCRN is not open to commercial enterprise and access is restricted to individuals working non-commercially in the field of critical care research. Mahesh Ramanan is currently the Chair of QCCRN (term July 2019-June2021).

Author contributions
Conceptualisation: MR, PK, SP, LB and BV. Data curation: MR, AA. Formal analysis: MR, LB. Investigation: MR, AA, LM, NB, DS, GR, RP, MP, PG. Methodology: MR, LM, PK, SP, LB and BV. Project administration: MR, BV. Resources: MR, AA. Validation: MR, BV. Writing—original draft: MR. Writing—review and editing: All authors. Supervision: BV, SP.

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Availability of data and material
Deidentified data are available for sharing. To request data, please contact the corresponding author with a request. This will be reviewed by the trial management committee. Applications from investigators with the suitable academic capability to conduct the proposed work will be given consideration. Any proposal will require approval from the ethics committee which approved the conduct of this trial prior to sharing of any patient data. If a proposal is approved, a signed data transfer agreement will be required before data sharing.

Code availability
Not applicable.

Declarations

Conflicts of interest
The authors do not have any conflicts of interest or competing interests to declare.

Ethics approval (include appropriate approvals or waivers)
Ethics approval was granted by the Royal Brisbane and Women's Hospital Human Research Ethics Committee (HREC/2018/QRBW/43868) for this trial to be conducted at all participating sites with a full consent waiver.

Consent to participate
Full consent waiver was approved by the Ethics Committee.

Consent for publication
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