Critical Care and Resuscitation 27 (2025) 100104

Contents lists available at ScienceDirect

Critical Care and Resuscitation

journal homepage: www.elsevier.com/locate/ccrj

Original Article

Buffered salt solution versus 0.9% sodium chloride as fluid therapy for patients presenting with moderate to severe diabetic ketoacidosis: Study protocol for a Phase-3 cluster-crossover, blinded, randomised, controlled trial

Mahesh Ramanan, FCICM, MMed [a, b, c, *], Dorrilyn Rajbhandari, PGDip Clin Nurs [b], Carolyn Koch, RN PGDip ICU [b], Yasmine Ali Abdelhamid, FCICM, FRACP, PhD [d, e], Antony Attokaran, FCICM, FRACP, MBBS [f, g], Laurent Billot, AStat, MRes [h, i], Severine Bompoint, AStat [j], Jeremy Cohen, FCICM, PhD [j, k, l], Anthony Delaney, FCICM, FACEM, PhD [b, m], Anthony Devaux, PhD [j], Elif Ekinci, FRACP, PhD [n, o], Simon Finfer, FCICM, DrMed [b, m, p], Tessa Garside, FCICM, PhD [m, q], Naomi Hammond, RN, PhD [b, r], Alisa Higgins, PhD [b, s], Gerben Keijzers, FACEM, PhD [t, u, v], Qiang Li, AStat, MBiostat [j], Benjamin Moran, FCICM, FANZCA, MBiostat [b, w, x], John Myburgh, FCICM, PhD [b, y], Priya Nair, FCICM, PhD [z], Sandra Peake, FCICM, PhD [aa, ab], Anthony Russell, FRACP, PhD [ac], Alexis Tabah, FCICM, MD [c, ad], Stacey Watts, RN GradCert Crit Care [ae], Balasubramanian Venkatesh, FCICM, MD [b, af]

[a] *Intensive Care Services, Caboolture and Royal Brisbane and Women's Hospital, Brisbane, Queensland, Australia;* [b] *Critical Care Division, The George Institute for Global Health, University of New South Wales, Sydney, New South Wales, Australia;* [c] *Faculty of Health, Queensland University of Technology, Brisbane, Queensland, Australia;* [d] *Intensive Care Unit, Royal Melbourne Hospital, Parkville, Victoria, Australia;* [e] *University of Melbourne, Melbourne Medical School, Department of Critical Care, Parkville, Victoria, Australia;* [f] *Intensive Care Unit, Rockhampton Hospital, Rockhampton, Queensland, Australia;* [g] *Rural Clinical School, University of Queensland, Rockhampton, Queensland, Australia;* [h] *Statistics Division, The George Institute for Global Health, University of New South Wales, Sydney, New South Wales, Australia;* [i] *Faculty of Medicine, University of New South Wales, Sydney, New South Wales, Australia;* [j] *The George Institute for Global Health, University of New South Wales, Sydney, New South Wales, Australia;* [k] *School of Medicine, University of Queensland, St Lucia, Brisbane, Queensland, Australia;* [l] *The Wesley and Royal Brisbane and Women's Hospital, Brisbane, Queensland, Australia;* [m] *Intensive Care Department, Royal North Shore Hospital, St Leonards, New South Wales, Australia;* [n] *Melbourne Medical School, University of Melbourne, Parkville, Victoria, Australia;* [o] *Austin Health, Heidelberg, Victoria, Australia;* [p] *School of Public Health, Faculty of Medicine, Imperial College London, London, UK;* [q] *University of Sydney, Sydney, New South Wales, Australia;* [r] *Royal North Shore Hospital, St Leonards, New South Wales, Australia;* [s] *Australia New Zealand Intensive Care Research Centre, School of Public Health and Preventive Medicine, Monash University, Victoria, Australia;* [t] *Emergency Department, Gold Coast University Hospital, Gold Coast, Australia;* [u] *School of Medicine, Griffith University, Gold Coast, Australia;* [v] *Faculty of Health Sciences and Medicine, Bond University, Gold Coast, Queensland, Australia;* [w] *Department of Intensive Care and Department of Anaesthesia and Pain Medicine, Gosford Hospital, Gosford, New South Wales, Australia;* [x] *School of Medicine and Public Health, University of Newcastle, Callaghan, New South Wales, Australia;* [y] *Intensive Care Department, St George Hospital, Kogarah, New South Wales, Australia;* [z] *Intensive Care Services, St Vincent's Hospital Sydney, Darlinghurst, New South Wales, Australia;* [aa] *Intensive Care Unit, The Queen Elizabeth Hospital, Woodville, South Australia, Australia;* [ab] *School of Medicine, University of Adelaide, Adelaide, South Australia, Australia;* [ac] *School of Public Health and Preventative Medicine, Monash University, Clayton, Victoria, Australia;* [ad] *Intensive Care Unit, Redcliffe Hospital, Redcliffe, Queensland, Australia;* [ae] *Department of Emergency Medicine, Caboolture Hospital, Caboolture, Queensland, Australia;* [af] *Gold Coast University Hospital, Southport, Queensland, Australia*

ARTICLE INFORMATION

Article history:
Received 13 September 2024
Received in revised form
10 February 2025
Accepted 11 February 2025

Keywords:
Diabetic ketoacidosis

ABSTRACT

Background: The optimal choice of fluid therapy for patients with diabetic ketoacidosis (DKA) is uncertain, though preliminary data suggest that buffered crystalloid solutions (Plasma-Lyte® 148) may offer some advantages over 0.9% saline.

Objective: To describe the study protocol for the 'Balanced Electrolyte Solution versus Saline Trial for Diabetic Ketoacidosis' (BEST-DKA) trial.

Design, setting and participants: BEST-DKA is a Phase 3 cluster-crossover, blinded, pragmatic, randomised, controlled trial comparing the effects of saline or buffered crystalloid solution in patients with moderate to severe DKA treated in the emergency department and/or intensive care unit at

* Corresponding author at: Critical Care Division, The George Institute for Global Health, Australia.
E-mail addresses: Mahesh.ramanan@health.qld.gov.au, mramanan@georgeinsitute.org.au (M. Ramanan).

https://doi.org/10.1016/j.ccrj.2025.100104

Diabetes
Fluid
Critical care
Emergency

twenty hospitals in Australia. Each hospital will be randomised to use either saline or buffered crystalloid solution for a period of 12 months before crossing over to the alternate fluid for the next 12 months. The blinded study fluid will be used for all resuscitation and maintenance purposes for included patients.

Main outcome measures: This cluster-randomised, crossover randomised controlled trial (RCT) has been designed with the aim of enrolling a minimum of 400 patients, which will provide >91.4% power to detect a 2-day increase in the primary outcome, days alive and out of hospital to day 28, chosen with consumer representation. Secondary outcomes include quality of life and fatigue scores at day 28, intensive care unit and hospital lengths of stay, acute kidney injury, and time to resolution of DKA. All analyses will be conducted on an intention-to-treat basis. A prespecified statistical analysis plan will be developed prior to interim analysis.

Results and conclusion: The BEST-DKA trial commenced enrolment in March 2024 and should generate results that will determine whether treatment with Plasma-Lyte® 148, compared with saline, results in increased days alive, and out of hospital to day 28 for patients with moderate or severe DKA.

1. Introduction

Diabetic ketoacidosis (DKA) is a life-threatening complication of diabetes mellitus, described in patients with both type 1 diabetes, and type 2 diabetes.[1] There are >7000 patients hospitalised annually in Australia alone with DKA.[2] Data from the Australian Institute of Health and Welfare suggest that between 2009 and 2015, there has been a 21% increase in the hospitalisation amongst young people with DKA.[2] The incidence of intensive care unit (ICU) admission for DKA in Australia has increased 5-fold from 0.97/100,000 in 2000 to 5.3/100,000 in 2013.[3] There were 2849 and 2862 ICU admissions with DKA in 2019 and 2020, respectively.[4]

Patients with DKA present with hyperglycaemia, severe dehydration and a high anion gap metabolic acidosis due to the accumulation of ketoacids in the plasma. Intravenous fluid replacement and insulin therapy remain cornerstones of therapy. The therapeutic goals of fluid management are directed at correcting dehydration and hypovolaemia over the first 24–48 h, reducing serum osmolality and plasma glucose concentrations towards normal levels, improving glomerular filtration rate to enhance ketone clearance, correcting electrolyte imbalances (such as avoiding hypokalaemia), and limiting the risk of complications such as cerebral oedema.[5–8]

Current international guidelines recommend 0.9% sodium chloride (saline) as the replacement fluid of choice, although no robust data from randomised controlled trials (RCTs) support these recommendations.[7–10] The rationale for using saline is based on historical and anecdotal preferences, its efficacious restoration of the circulating volume and improvement of tissue perfusion. There is substantial variability in practice, which is reflective of the lack of high-quality RCT data.[11–14]

However, if saline is administered rapidly and volumes greater than 2L as typically seen in DKA,[15,16] the nonphysiologic chloride concentration of saline as compared to plasma (154 vs 100 mmol/L) leads to hyperchloraemia, which can further worsen the metabolic acidosis.[17] This cohort study also demonstrated that the incidence of hyperchloraemic acidosis progressively increases from 6% at the start of DKA treatment to 94% after 20 h of treatment.[17]

A high serum chloride concentration may have other important adverse effects.[18] A meta-analysis of high chloride vs low chloride fluid resuscitation in perioperative and critical care patients reported that 0.9% saline was associated with a higher risk of acute kidney injury (AKI), metabolic acidosis and increased duration of mechanical ventilation.[19] A recent individual-patient-data Bayesian meta-analysis demonstrated 82% probability of reduced need for renal replacement therapy for critically ill patients treated with balanced solution compared to saline.[20]

Balanced crystalloid solutions, such as Plasma-Lyte® 148, have sodium and chloride concentrations that more closely approximate human plasma.[21] The use of Plasma-Lyte® 148 as fluid therapy for patients with DKA, compared to 0.9% saline, may have several benefits, including lower risk of hyperchloraemic acidosis, faster resolution of metabolic acidosis and shorter ICU and hospital stay while maintaining similar normalisation of blood glucose and ketones.[22–24] A subgroup analysis of two cluster-randomised trials showed that patients treated with balanced crystalloid solutions, compared to saline, had significantly shorter time to DKA resolution and time on intravenous insulin infusion, while other outcomes, such as ICU- and hospital-free days, were similar.[23] A Phase-2 cluster-crossover RCT showed that treatment with Plasma-Lyte® 148 resulted in a significantly shorter time to resolution of metabolic acidosis and trends towards shorter ICU and hospital length of stay.[22] A meta-analysis of eight RCTs demonstrated that in addition to shorter time to DKA resolution, lower serum chloride, and higher serum bicarbonate, treatment with balanced crystalloids resulted in significantly shorter hospital length of stay.[24]

However, there have been no large, adequately powered randomised trials that demonstrate clinically meaningful benefits in patient-important outcomes with the use of Plasma-Lyte® 148 compared to 0.9% saline for patients with DKA.

To address this evidence gap, we have designed the 'Balanced Electrolyte Solution versus Saline Trial for Diabetic KetoAcidosis (BEST-DKA)'. The primary hypothesis is that in patients admitted to a critical care area with moderate to severe DKA, fluid therapy with Plasma-Lyte® 148, compared with 0.9% saline, will lead to increased days alive and out of hospital to day 28 postenrolment.

2. Methods

2.1. Trial management

The BEST-DKA trial is an investigator-initiated trial sponsored by The George Institute for Global Health. It is funded by grants from the Medical Research Future Fund (MRFF2030670), Emergency Medicine Foundation, Queensland (EMPJ-271R39-2023-KEIJZERS), Diabetes Australia (Y24M1-RUSA), and an unrestricted grant from Baxter Healthcare to fund the production and delivery of blinded trial fluid. Neither the sponsor nor any of the funders have had any input into trial design and conduct. They will not have any role in analysis, interpretation, and manuscript writing once the trial recruitment has completed.

BEST-DKA is endorsed by the Australia New Zealand Intensive Care Society Clinical Trials Group. It was prospectively registered on clinicaltrials.gov (NCT05752279). This protocol is reported according to the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) statement 2013.[25]

2.2. Ethics and consent

Ethics approval was granted by the Metro North Human Research Ethics Committee 'A' (approval number: HREC/2022/MNHA/91605;) with waiver of consent for enrolment of participants based on Section 2.3.10 of the National Statement on Ethical Conduct in Human Research.[26] Briefly, the waiver was requested on the basis that patients with moderate to severe DKA are often unable to provide informed consent at the time of presentation due to the severity of the acute illness, and they require time-critical resuscitation, which includes substantive volumes of intravenous fluids. It would be considered entirely unethical to withhold fluids in this circumstance, and thus we requested a waiver of consent to include patients in the study and provide fluids as per the study allocation.

Written informed consent for the use of any data and the day 28 follow-up will be obtained from the patient or their surrogate decision maker prior to hospital discharge. Patients, or their surrogate decision-makers, will also be given the opportunity to freely withdraw from the study. Where consent to continue participation is declined or withdrawn, usual care is provided, and no patient data are obtained, unless specific consent to do so is obtained.

2.3. Trial design

BEST-DKA is a multicentre, blinded, cluster-crossover trial conducted in 20 Australian hospitals, consisting of two consecutive 12-month intervention periods with a one-month inter-period gap.

Each hospital is a single cluster, with all patients admitted with moderate to severe DKA to that hospital's emergency department (ED) during the intervention periods potentially eligible for inclusion in the trial. After the first 12-month intervention period, during which recruited patients will receive either Plasma-Lyte® 148 or 0.9% saline in a blinded fashion, according to the allocation schedule, there will be a one-month inter-period gap during which patients will not be recruited into the trial. Following this, each hospital will change to using the alternative fluid for the second 12-month intervention period (Fig. 1).

2.4. Participants

Adult patients (age $\geq$ 18 years) will be eligible for enrolment into BEST-DKA if they meet all the inclusion and none of the exclusion criteria listed in Table 1. The American Diabetes Association criteria for moderate and severe DKA will be used to identify the study population, which includes blood glucose>14 mmol/L, pH < 7.25, serum bicarbonate<15 mmol/L, anion gap>12 mmol/L, and positive ketones on capillary blood.[27]

A critical care area for the purpose of this trial will include ICUs as defined by the College of Intensive Care Medicine of Australia and New Zealand,[28] or a high acuity area within an emergency department (ED) where higher-level supports, including invasive monitoring, frequent blood gas analyses, and other resuscitative measures can be provided. Practically, this may include environments such as a resuscitation bay, or other appropriately monitored area.

2.5. Allocation and randomisation

Participating hospitals will be randomised using randomly generated computer tables, generated by the trial statistician, in a 1:1 ratio. Each hospital is blinded to the study fluid allocated for each intervention period. All critical care areas within each hospital will be part of the same cluster.

Potential participants will be identified and screened by ED or ICU clinicians for study eligibility. A screening log will be kept to monitor recruitment and report the size of the patient population from which eligible patients have been recruited. All patients who

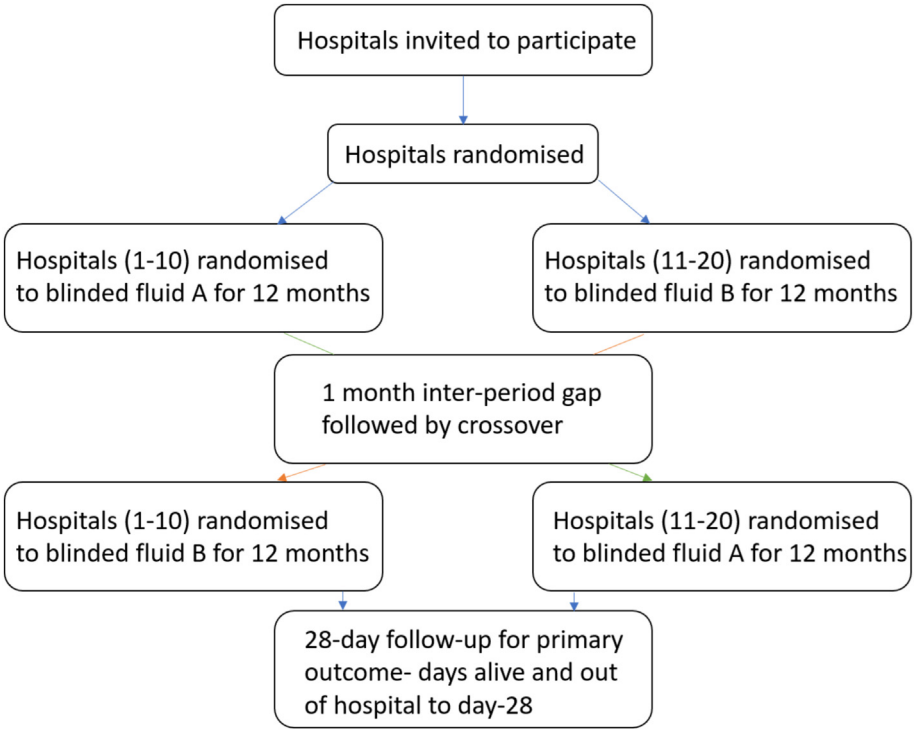

Fig. 1. Study flowchart.

Table 1
Inclusion and exclusion criteria.

Inclusion criteria
- Patients in the ED with a primary diagnosis of moderate to severe DKA as defined by: • Blood glucose level >14 mmol/L • pH < 7.25 • Serum bicarbonate <15 mmol/L • Elevated anion gap >12 mmol/L • Ketones positive on finger prick measurements - In the judgement of the treating clinician, both saline and Plasma-Lyte are considered appropriate fluids - In the judgement of the treating clinician critical care area admission is required
Exclusion criteria
- Age less than 18 years - Patients who have received more than 2000 mL of nonstudy fluid prior to study enrolment - Serum sodium concentration >155 or <120 mmol/L (uncorrected) - Contraindication to either study fluid e.g. previous allergic reaction to Plasma-Lyte® 148 - Patients with hyperosmotic hyperglycaemic nonketotic syndrome - Other clinical conditions that preclude large volumes of fluid resuscitation - Previous inclusion in BEST-DKA trial within the last 28 days

ED-emergency department; DKA-diabetic ketoacidosis; BEST-DKA- 'Balanced Electrolyte solution versus Saline Trial for Diabetic KetoAcidosis'.

were admitted to the ED at participating hospitals meeting all the inclusion criteria and no exclusion criteria will be enrolled in the study. Enrolment will be via a password-protected, encrypted web-based interface. Each enrolled patient will be assigned a unique 'patient study number'. Each participant will receive the study fluid allocated to the particular hospital for that timeframe, either Plasma-Lyte 148 or 0.9% saline.

2.6. Study interventions and procedures

BEST-DKA study fluids will be started whilst the participant is in the ED. The study treatments will be supplied in identical 1000 mL bags with standardised fluid administration sets without revealing the fluid type. Both fluids are colourless, clear solutions and macroscopically indistinguishable. Both participants and study investigators will be blinded to study treatment allocation.

Both study fluids are manufactured by Baxter Healthcare Pty Ltd (Old Toongabbie, New South Wales, Australia) and will be labelled as 'BEST-DKA Fluid (A or B)', packed and distributed by the company directly to the study sites in periodic shipments. Study fluid will be coded and labelled in compliance with applicable regulations and in a manner that protects the blinding. The two study fluids will be presented in identically labelled fluid bags, which will be indistinguishable to clinicians (Fig. 2).

Management of fluid storage and allocation will be determined on a site-by-site basis and designed to maximise protocol adherence and avoid both wastage and unintended use of nonstudy fluids. Study fluids must be stored below 30 C.

The volume and rate of blinded study fluid administered will be determined by the treating clinician. Study treatments will be started immediately following study enrolment and continue until discharge from a critical care area or for a maximum of 72 h, whichever is earlier. If patients are readmitted to the critical care area within 72 h with a relapse of ketoacidosis, clinicians will use open-label fluids for the managements of ketoacidosis. Glucose-containing solutions can be administered as required for blood glucose or ketosis management. The use of bicarbonate therapy and the need for potassium, phosphate, and magnesium supplementation will be at the discretion of the treating clinician and data on their use will be collected.

Other crystalloid fluids may be used as carrier fluids for the infusion of any drug for which either Plasma-Lyte® 148® and/or

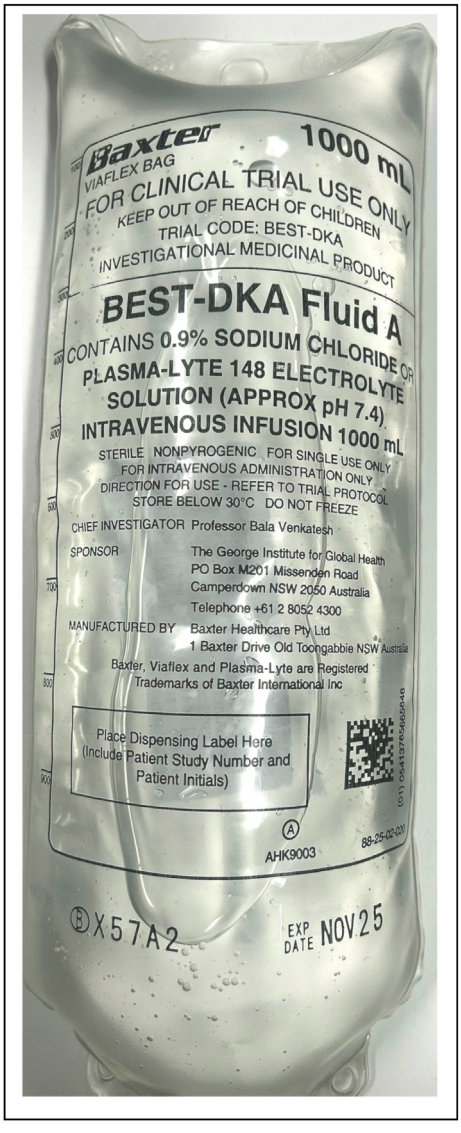

Fig. 2. Blinded study fluid.

0.9% saline is considered incompatible; in such instances, 5% glucose should be used whenever possible.

Aside from the study treatment, patient management will be at the discretion of the treating clinicians, who will be free to provide whatever medical care is deemed best and necessary for the patient.

If patients, whilst still receiving study fluids, undergo a surgical intervention, it will be recommended that blinded trial fluid be continued during that period. Where specific intravenous fluid solutions become clinically indicated, the appropriate fluid will be allowed by the protocol as directed by the treating clinicians. All study and nonstudy fluids administered will be recorded.

2.7. Data collection and management

Study participants will be followed-up for 28 days from enrolment into the study (Fig. 3).

Data collection will be conducted by trained staff at each participating site and will be entered into RedCap[29,30] electronic case report forms with data stored on secure servers at The George Institute for Global Health. Information collected will include eligibility criteria at enrolment, baseline patient demographics and clinical data. During the first 72 h in a critical care area, information on daily physiological parameters, biochemistry, and treatment will be collected. At 28 days after enrolment, information on vital status, hospital readmissions, quality-of-life using the EuroQOL EQ-5D-5L questionnaire,[31] and fatigue using the Modified Fatigue Score,[32] will be obtained via email or telephone. A screening log will be maintained at each participating site to record patients who were admitted with DKA but were considered ineligible.

2.8. Outcomes

Days alive-and-out-of-hospital up to 28 days (DAH-28) after study enrolment will be the primary outcome. A consumer representative was involved in the selection of this patient-centred primary outcome. In DKA, the primary determinants of clinical recovery from illness are the resolution of acidosis and correction of dehydration. In discussion with our consumer representative, a shorter length of hospital stay is an important patient-centred outcome, as this would not only reflect improving physical health but also have a positive psychosocial impact. This is particularly relevant to people living with type 1 diabetes, as hospitalisation is typically associated with diabetes distress.[33] This outcome has also been endorsed by the Australia New Zealand Intensive Care Society Clinical Trials Group as a patient-centred outcome for use in critical care clinical trials.[34]

All outcomes and their definitions are listed in Table 2.

2.9. Sample size calculations

There were 20 clusters (i.e., hospitals) in each interventional period at the start of the trial, with a further two clusters added during the first interventional period due to lower than expected recruitment in some clusters. Based on Phase II data from the SCOPE-DKA trial,[22] the average enrolment per cluster is expected to be 10–12 patients per 12-month intervention period. Over the 2 periods, 20–24 patients per cluster are expected to be enrolled, generating an anticipated sample size range between 400 and 480 patients. The final sample will be determined by the actual number of patients admitted and enrolled in each cluster.

Task	Screening	Enrolment	Baseline	0 – 72 hours	Day 28
Assess eligibility to enter study	X				
Demographics & eligibility checklist		X			
Laboratory Data: blood gas, plasma beta hydroxybutyrate, fingerstick capillary ketones, biochemistry (electrolytes and renal),			X	X	
Clinical Data: HR, BP, RR, temp, GCS and APACHE score			X	X	
Administer study treatment & study treatment reconciliation				X	
Provision of patient information brochure & withdrawal of consent form				X	X
Written consent for Day 28 follow up contact				X	
Interventions: Insulin infusion, potassium, bicarbonate, phosphate and magnesium replacement, mechanical ventilation, vaso-active infusion, renal replacement therapy, central venous catheter, arterial catheter				X	X
Adverse Reactions				X	X
Protocol Deviations				X	X
Day 28: hospital and ICU discharge and readmissions, follow-up email and phone call, vital status, Questionnaires; EQ-5D-5L, Modified Fatigue Impact Scale					X

Fig. 3. Study assessments schedule. HR-heart rate; BP- blood pressure; RR-respiratory rate; GCS- Glasgow coma score; APACHE-acute physiology and chronic health evaluation; ICU- intensive care unit; EQ-5D-5L- EuroQOL five dimension five level scale.

Table 2
Outcomes.

Primary outcome
Days alive and out of hospital to day 28 after study enrolment Calculated as 28 minus the total number of days spent as an inpatient in any hospital during the first 28 days from the date of study enrolment. This includes the index hospital admission and any hospital readmissions during the 28-day follow-up period. Patients who die during the 28-day follow-up period will be assigned '0'. Any part of a day spent as an inpatient in a hospital will count as one day.
Secondary outcomes
Days alive and out of ICU up to 28 days after study enrolment Calculated as 28 minus the total number of days spent as an inpatient in any ICU during the first 28 days from the date of study enrolment. This includes days spent in ICU during the index hospital admission and during any hospital readmissions during the 28-day follow-up period. Patients who die during the 28-day follow-up period will be assigned '0'. Any part of a day spent as an inpatient in an ICU will count as one day. ICU and hospital readmissions up to 28 days after study enrolment (number of readmissions) Acute kidney injury assessed by comparing serum creatinine using Kidney Disease: Improving Global Outcomes (KDIGO) criteria[35] (number of patients in each category) Episodes of postrandomisation unsedated decrease in Glasgow Coma Score (GCS) by more than 2 in the first 24 h (number of episodes) Time to resolution (<1 mmol/L) of ketosis (hours) Cumulative insulin dosage in the first 48 h (units) Duration of intravenous insulin infusion in the ICU (hours) Cumulative potassium replacement in the first 48 h (mmol) Proportion of patients with hypokalaemia (serum potassium concentration <3.5 mmol/L) Quality of life 28 days after study enrolment as measured by the EuroQoL 5D-5L[31] instrument Modified fatigue score[32] 28 days after study enrolment
Process measures
Serum acetoacetate and β-hydroxybutyrate concentrations at 6, 12, 24, and 48 h Serum base excess at 6, 12, 24, and 48 h Serum sodium, potassium, and chloride concentration at 6, 12, 24, and 48 h
Tertiary outcome
Cost-effectiveness analysis

Based on data from our Phase II study (mean days alive and out of the hospital to day 28 = 21.4 days, SD 6.46 in 0.9% saline group and 23.3 days, SD 3.86, in Plasma-Lyte® 148 group), we have at least 90% power to identify a difference of +2.0 DAH-28 for the Plasma-Lyte® 148 group versus the 0.9% saline group, if we enrol between 400 and 480 patients.

These calculations are based on a level of alpha = 0.05 and assume an exchangeable correlation structure with an intra-cluster coefficient of 0.01. This study size allows for a potential withdrawal and loss to follow-up rate of 1% (based on the recently completed large-scale ICU trials[36]) with negligible effect on study power.

2.10. Statistical analysis

All analyses will be conducted on an intention-to-treat basis using standard statistical methods for continuous and categorical data. The primary outcome will be analysed using a mixed model considering the cluster effect, number of times patients are enrolled, and sequence allocation. Time to hospital discharge will be analysed using a survival analysis with death as a competing risk (and robust standard errors at cluster level). Predefined subgroups will include Type I vs Type II diabetes, severity of acidosis defined by admission pH of 7.00–7.25 or pH < 7.0 and by volume and type of open-label prerandomisation fluids. Pre-specified hypotheses and underlying rationale for the subgroups are presented in Table 3. Analyses will be based on complete-case sets, but a multiple imputation approach to deal with missing data will be considered according to the magnitude and patterns of missing data. A statistical analysis plan will be finalised, published, and be publicly available before database lock.

We will undertake an updated systematic review and meta-analysis and collaborate with other investigator groups for an individual patient data meta-analysis.

2.11. Cost-effectiveness analysis

The primary cost-effectiveness analysis will be conducted from the Australian healthcare payer's perspective using a within-trial analytical time horizon of 28 days. We will calculate incremental cost-effectiveness ratios, including the cost per hospital bed day saved and the cost per ICU bed day saved for Plasma-Lyte® 148 compared to 0.9% saline. Assessment of resource use will be restricted to the index hospital admission. We will calculate the cost of hospital admissions using data on ICU and hospital length of stay using published Australian data. To increase the robustness of the sampling distribution, we will use nonparametric bootstrapping with unrestricted random sampling to produce cost and effectiveness replications, and confidence intervals for the cost-effectiveness ratios.

2.12. Interim analysis

All adverse events thought to be related to the study treatment will be reported to the coordinating centre (The George Institute for Global Health). These will be recorded in the study database and reported to the Data Safety Management Committee (DSMC). The DSMC will be independent from the coordinating centre and the investigators and will perform a review of predefined safety parameters, study outcomes, and overall study conduct.

The DSMC is comprised of experts in clinical trials, endocrinology, biostatistics, and critical care. One interim analysis will be conducted by the DSMC at the end of the first study period after all patients enrolled have completed their 28-day follow-up. Additional analyses and safety reviews will be performed at the discretion of the DSMC. A DSMC charter has been developed based on the 'DAta MOnitoring Committees: Lessons, Ethics, Statistics' statement[37] outlining roles, responsibilities, reporting, communication, and stopping rules for harm, benefit and futility, and has been signed by the chairperson and all members of the DSMC.

Table 3
Prespecified subgroup analyses.

Category	Subgroups	Hypothesis	Rationale
Severity of acidosis	Admission pH < 7.00 vs pH 7.00–7.25	Patients with pH < 7.00 will have greater benefit with Plasma-Lyte® 148	Patients with more severe acidosis may benefit more from the alkalinising effect of Plasma-Lyte® 148
Diabetes type	Type 2 vs type 1 diabetes	Patients with type 2 diabetes will have greater benefit with Plasma-Lyte® 148	Patients with type 2 diabetes tend to be older, have more comorbidity, more renal dysfunction, and hence tendency towards more severe acidosis
Type of pre-enrolment fluid	Saline vs buffered salt solutions	Patients treated with pre-enrolment saline will have worse outcomes than those treated with Plasma-Lyte® 148	Patients treated with pre-enrolment saline will tend to have more hyperchloraemic acidosis
Volume of pre-enrolment saline	≥1L of saline vs <1L of saline as pre-enrolment fluid	Patients treated with larger volumes of pre-enrolment saline will have worse outcomes than those treated with Plasma-Lyte® 148	Patients treated with larger volumes of pre-enrolment saline will tend to have more hyperchloraemic acidosis

2.13. Monitoring

The coordinating centre is responsible for taking all reasonable steps to ensure proper conduct of the clinical trial protocol. The George Institute for Global Health will provide all aspects of trial management, operations, and monitoring.

The coordinating centre monitor/s will visit each study site on multiple occasions during the recruitment phase to evaluate compliance with study protocol, Good Clinical Practice guidelines, and other regulatory requirements. The study may be audited by local or national regulatory authorities. Source documents and all study files will be made available at study sites for monitoring and auditing purposes. Source data verification by trained monitors for all informed consent forms and for the primary outcome and protocol compliance on 10% of all patients will be carried out. The coordinating centre team will conduct regular remote monitoring on the web-based database by applying validation and consistency rules and with regular data cleaning to ensure the integrity of the study data.

2.14. Close out

At the completion of the study, there will be plans for long-term storage of study data and source documents for 15 years, as per the ethics approval. The study fluids will be reconciled and disposed of, as per standard procedures at the individual sites.

2.15. Current status

The BEST-DKA trial commenced recruitment on 14/03/2024 and is enrolling participants at the expected rate.

2.16. Summary

BEST-DKA is an investigator-initiated, multicentre, blinded, cluster-crossover trial conducted in 20 Australian hospitals to determine whether fluid therapy with Plasma-Lyte® 148 compared to 0.9% saline results in increased days alive and out of hospital to day 28 for patients with moderate or severe DKA.

CRediT authorship contribution statement

Conception and design: Balasubramanian Venkatesh, Mahesh Ramanan.

Funding acquisition: All authors.

Oversight/Supervision: Balasubramanian Venkatesh.

Manuscript first draft: Mahesh Ramanan, Dorrilyn Rajbhandari, Balasubramanian Venkatesh.

Manuscript review and editing: all authors.

Funding statement

Medical Research Future Fund (MRFF2030670).
Emergency Medicine Foundation (EMPJ-271R39-2023-KEIJZERS).
Diabetes Australia (Y24M1-RUSA).
Baxter Healthcare.

Conflict of interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Mahesh Ramanan reports financial support for BEST-DKA was provided by Medical Research Futures Fund. Gerben Keijzers reports financial support for BEST-DKA was provided by Emergency Medicine Foundation. Anthony Russell reports financial support for BEST-DKA was provided by Diabetes Australia. Balasubramanian Venkatesh reports financial support and equipment, drugs, or supplies for BETS-DKA were provided by Baxter Healthcare Ltd. Elif Ekinci reports clinical trial funding from Eli Lilly, Novo Nordisk, Boehringer-Ingelheim, Versanic, Amgen, Novartis and Endogenex. Elif Ekinci sits on advisory boards and given presentations for Bayer, Eli Lilly, Astra Zeneca, Boehringer and these funds are donated to her institution for diabetes research. The other authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data safety monitoring committee

Professor Anders Perner (chair): experienced critical care clinical trialist.

Professor Jonathon Shaw: experienced endocrinology clinical trialist.

Professor Marion Campbell: expert biostatistician.

Participating hospitals

Ballarat Base Hospital.
Blacktown Hospital.
Caboolture Hospital.
Campbelltown Hospital.
Casey Hospital.
Dandenong Hospital.
Dubbo Base Hospital.
Frankston Hospital.
Gold Coast University Hospital.
Latrobe Regional Hospital.

Lyell McEwin Hospital.
Maitland Hospital.
Orange Base Hospital.
Queen Elizabeth II Jubilee Hospital.
The Queen Elizabeth Hospital.
Redcliffe Hospital.
Rockhampton Hospital.
Royal North Shore Hospital.
St George Hospital.
Sunshine Coast University Hospital.
Wagga Wagga Base Hospital.
Westmead Hospital.

References

[1] Umpierrez GE. Ketosis-prone type 2 diabetes: time to revise the classification of diabetes. Diabetes Care 2006;29(12):2755–7. https://doi.org/10.2337/dc06-1870.
[2] Australian Institute of Health and Wefare. Diabetic ketoacidosis (DKA) among children and young people with type 1 diabetes. 2016. p. 1–4.
[3] Venkatesh B, Pilcher D, Prins J, Bellomo R, Morgan TJ, Bailey M. Incidence and outcome of adults with diabetic ketoacidosis admitted to ICUs in Australia and New Zealand. Crit Care Lond Engl 2015;19:451. https://doi.org/10.1186/s13054-015-1171-7.
[4] ANZICS Centre for Outcome and Resource Evaluation. Centre for outcome and resource evaluation 2020 report. https://www.anzics.com.au/annual-reports/; 2020.
[5] Kitabchi AE, Umpierrez GE, Miles JM, Fisher JN. Hyperglycemic crises in adult patients with diabetes. Diabetes Care 2009;32(7):1335–43. https://doi.org/10.2337/dc09-9032.
[6] Savage MW, Dhatariya KK, Kilvert A, Rayman G, Rees J, Courtney C, et al. Joint British Diabetes Societies guideline for the management of diabetic ketoacidosis. Diabet Med J Br Diabet Assoc 2011;28(5):508–15. https://doi.org/10.1111/j.1464-5491.2011.03246.x.
[7] Joint British Diabetes Societies for Inpatient Care Group. The management of diabetic ketoacidosis in adults. 2013.
[8] Craig ME, Twigg SM, Donaghue KC, Cheung NW, Cameron FJ, Conn J et al. for the Australian Type 1 Diabetes Guidelines Expert Advisory Group. National evidence-based clinical care guidelines for type 1 diabetes in children, adolescents and adults, Published online 2011.
[9] Dhatariya K, Savage M, Claydon A, Dyer P, Evans P, Khan A, et al. The management of diabetic ketoacidosis in adults. Published online March 1, https://abcd.care/resource/current/jbds-02-management-diabetic-ketoacidosis-adults [Accessed 14 November 2024].
[10] Umpierrez GE, Davis GM, ElSayed NA, Fadini G, Galindo R, Hirsch I, et al. Hyperglycemic crises in adults with diabetes: a consensus report. Diabetes Care 2024;47(8):1257–75. https://doi.org/10.2337/dci24-0032.
[11] Dhatariya KK, Nunney I, Higgins K, Sampson MJ, Iceton G. National survey of the management of diabetic ketoacidosis (DKA) in the UK in 2014. Diabet Med J Br Diabet Assoc 2016;33(2):252–60. https://doi.org/10.1111/dme.12875.
[12] Fusco N, Gonzales J, Yeung SYA. Evaluation of the treatment of diabetic ketoacidosis in the medical intensive care unit. Am J Health-Syst Pharm AJHP Off J Am Soc Health-Syst Pharm. 2015;72(23 Suppl 3):S177–82. https://doi.org/10.2146/sp150028.
[13] Henriksen OM, Prahl JB, Røder ME, Svendsen OL. Treatment of diabetic ketoacidosis in adults in Denmark: a national survey. Diabetes Res Clin Pract 2007;77(1):113–9. https://doi.org/10.1016/j.diabres.2006.10.013.
[14] Barrios EK, Hageman J, Lyons E, Janies K, Leonard D, Duck S, et al. Current variability of clinical practice management of pediatric diabetic ketoacidosis in Illinois pediatric emergency departments. Pediatr Emerg Care 2012;28(12):1307–13. https://doi.org/10.1097/PEC.0b013e3182768bfc.
[15] Mårtensson J, Bailey M, Venkatesh B, Pilcher D, Deane A, Abdelhamid Y, et al. Intensity of early correction of hyperglycaemia and outcome of critically ill patients with diabetic ketoacidosis. Crit Care Resusc J Australas Acad Crit Care Med 2017;19(3):266–73.
[16] Scheingraber S, Rehm M, Sehmisch C, Finsterer U. Rapid saline infusion produces hyperchloremic acidosis in patients undergoing gynecologic surgery. Anesthesiology 1999;90(5):1265–70. https://doi.org/10.1097/00000542-199905000-00007.
[17] Adrogué HJ, Wilson H, Boyd AE, Suki WN, Eknoyan G. Plasma acid-base patterns in diabetic ketoacidosis. N Engl J Med 1982;307(26):1603–10. https://doi.org/10.1056/NEJM198212233072603.
[18] Shaw AD, Raghunathan K, Peyerl FW, Munson SH, Paluszkiewicz SM, Schermer CR. Association between intravenous chloride load during resuscitation and in-hospital mortality among patients with SIRS. Intensive Care Med 2014;40(12):1897–905. https://doi.org/10.1007/s00134-014-3505-3.
[19] Krajewski ML, Raghunathan K, Paluszkiewicz SM, Schermer CR, Shaw AD. Meta-analysis of high- versus low-chloride content in perioperative and critical care fluid resuscitation. Br J Surg 2015;102(1):24–36. https://doi.org/10.1002/bjs.9651.
[20] Zampieri FG, Cavalcanti AB, Di Tanna GL, Damiani L, Hammond N, Machado F, et al. Balanced crystalloids versus saline for critically ill patients (BEST-Living): a systematic review and individual patient data meta-analysis. Lancet Respir Med 2024;12(3):237–46. https://doi.org/10.1016/s2213-2600(23)00417-4.
[21] Weinberg L, Collins N, Van Mourik K, Tan C, Bellomo R. Plasma-Lyte 148: a clinical review. World J Crit Care Med 2016;5(4):235–50. https://doi.org/10.5492/wjccm.v5.i4.235.
[22] Ramanan M, Attokaran A, Murray L, Bhadange N, Stewart D, Rajendran G et al. Sodium chloride or Plasmalyte 148 evaluation in severe diabetic ketoacidosis (SCOPE DKA): a cluster, crossover, randomized, controlled trial. Intensive Care Med. Published online 2021. https://doi.org/10.1007/s00134-021-06480-5.
[23] Self WH, Evans CS, Jenkins CA, Bryan RM, Casey JD, Collins SP, et al. Clinical effects of balanced crystalloids vs saline in adults with diabetic ketoacidosis. JAMA Netw Open 2020;3(11):e2024596. https://doi.org/10.1001/jamanetworkopen.2020.24596.
[24] Alghamdi NA, Major P, Chaudhuri D, Tsui J, Brown B, Self W, et al. Saline compared to balanced crystalloid in patients with diabetic ketoacidosis: a systematic review and meta-analysis of randomized controlled trials. Crit Care Explor 2022;4(1):e0613. https://doi.org/10.1097/CCE.0000000000000613.
[25] Chan A, Tetzlaff J, Gøtzsche PC, Altman DG, Mann H, Berlin JA, et al. SPIRIT 2013 Statement: defining standard protocol items for clinical trials. Ann Intern Med 2013;158:200–7.
[26] National statement on ethical conduct in human research. Published online updated 2018. https://www.nhmrc.gov.au/about-us/publications/national-statement-ethical-conduct-human-research-2007-updated-2018 [Accessed 21 September 2022].
[27] Gosmanov AR, Gosmanova EO, Kitabchi AE. Hyperglycemic crises: diabetic ketoacidosis and hyperglycemic hyperosmolar state. In: Feingold KR, Anawalt B, Blackman MR, et al., editors. Endotext. MDText.com, Inc.; 2021. http://www.ncbi.nlm.nih.gov/books/NBK279052/ [Accessed 12 September 2023].
[28] College of Intensive Care Medicine. Minimum standards for intensive care units. 2011. p. 1–14.
[29] Harris PA, Taylor R, Thielke R, Payne J, Gonzalez N, Conde JG. Research electronic data capture (REDCap)–a metadata-driven methodology and workflow process for providing translational research informatics support. J Biomed Inf 2009;42(2):377–81. https://doi.org/10.1016/j.jbi.2008.08.010.
[30] Harris PA, Taylor R, Minor BL, Payne J, Gonzalez N, Conde JG, et al. The REDCap consortium: building an international community of software platform partners. J Biomed Inf 2019;95:103208. https://doi.org/10.1016/j.jbi.2019.103208.
[31] Herdman M, Gudex C, Lloyd A, Janssen M, Kind P, Parkin D, et al. Development and preliminary testing of the new five-level version of EQ-5D (EQ-5D-5L). Qual Life Res Int J Qual Life Asp Treat Care Rehabil. 2011;20(10):1727–36. https://doi.org/10.1007/s11136-011-9903-x.
[32] Larson RD. Psychometric properties of the modified fatigue impact scale. Int J MS Care 2013;15(1):15–20. https://doi.org/10.7224/1537-2073.2012-019.
[33] Skinner TC, Joensen L, Parkin T. Twenty-five years of diabetes distress research. Diabet Med J Br Diabet Assoc 2020;37(3):393–400. https://doi.org/10.1111/dme.14157.
[34] Young P, Hodgson C, Dulhunty J, Saxena M, Bailey M, Bellomo R, et al. End points for phase II trials in intensive care: recommendations from the Australian and New Zealand Clinical Trials Group consensus panel meeting. Crit Care Resusc J Australas Acad Crit Care Med 2012;14(3):211–5.
[35] Cook D, Deane A, Lauzier F, Zytaruk N, Guyatt G, Saunder L, et al. Stress ulcer prophylaxis during invasive mechanical ventilation. N Engl J Med 2024;391(1):9–20. https://doi.org/10.1056/NEJMoa2404245.
[36] DAMOCLES Study Group, NHS Health Technology Assessment Programme. A proposed charter for clinical trial data monitoring committees: helping them to do their job well. Lancet Lond Engl 2005;365(9460):711–22. https://doi.org/10.1016/S0140-6736(05)17965-3.
[37] Kidney Disease: Improving Global Outcomes (KDIGO) Acute Kidney Injury Work Group. KDIGO clinical practice guideline for acute kidney injury. Kidney Int Suppl 2012;2:1. https://doi.org/10.1038/kisup.2012.1.