Study protocol for the Balanced Solution versus Saline in Intensive Care Study (BaSICS): a factorial randomised trial

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The administration of intravenous (IV) fluids to restore intravascular volume is one of the most common interventions in the intensive care unit. Saline (0.9% sodium chloride) is the most widely used crystalloid fluid worldwide. Nevertheless, experimental and clinical studies show that saline has deleterious effects on the kidneys, acid–base balance, electrolyte homoeostasis, tissue perfusion, the inflammatory response and coagulation parameters.

Plasma-Lyte 148 is a balanced crystalloid fluid with osmolality closer to human plasma and lower sodium and chloride concentrations compared with saline. Observational and small randomised studies suggest that balanced crystalloid fluids might be preferable to saline in critically ill patients. One of the putative mechanisms for the benefit of balanced solutions is their lower potential to cause hyperchloraemia, which, in turn, could be associated with increased inflammation and acute kidney injury (AKI).

Recently, the safety and efficacy of volume expansion with Plasma-Lyte 148 compared with saline were assessed in an exploratory, double-blind, cluster-randomised, double-crossover trial (the 0.9% Saline v Plasma-Lyte 148 for ICU Fluid Therapy [SPLIT] study). In this study, a median infusion of 2 L of Plasma-Lyte 148 or saline did not affect the risk of AKI (risk ratio [RR], 1.04; 95% CI, 0.80–1.36; \( P = 0.77 \)), the need for renal replacement therapy (RRT) (RR, 0.96; 95% CI, 0.62–1.50; \( P = 0.91 \)) or in-hospital mortality (RR, 0.88; 95% CI, 0.67–1.17; \( P = 0.40 \)). However, the SPLIT trial used a very low dose of study fluid (2 L over the ICU stay), did not select fluid used specifically for resuscitation and studied a relatively low-risk population (mean Acute Physiology and Chronic Health Evaluation [APACHE] II score, 14; overall AKI rate, 9%).

In addition to the type of fluid, there are wide regional variations in infusion rates and volumes prescribed as fluid boluses. The multicentre Fluid Challenges in Intensive Care study showed that crystalloid fluids represent the most common type of fluids used in a fluid challenge, typically administered as a bolus of 500 mL in less than 30 minutes. Nevertheless, it has been suggested that fluid bolus infusion rate, a neglected aspect of fluid management, may have important effects on physiological and clinical outcomes in ICU patients.

A prospective, randomised study in African children with severe infection showed that fluid boluses of saline or 5% albumin increased mortality compared with standard therapy without boluses. Interestingly, most of the excess mortality with rapid fluid resuscitation was attributed to cardiovascular

ABSTRACT

Background: The effectiveness and safety of balanced crystalloid fluids compared with saline (0.9% sodium chloride) as a fluid of choice in critically ill patients remain unclear. The effects of different fluid infusion rates on outcomes are also unknown.

Objectives: To test the hypothesis that a balanced crystalloid solution, compared with saline, decreases 90-day all-cause mortality among critically ill patients; and to test the hypothesis that slow, compared with rapid, infusion rate decreases 90-day mortality in this population of patients.

Methods: The Balanced Solution versus Saline in Intensive Care Study (BaSICS) is a pragmatic, 2 × 2 factorial, randomised controlled trial. A total of 11 000 patients will be recruited from at least 100 Brazilian intensive care units. Patients will be randomised to receive Plasma-Lyte 148 or saline, and to rapid infusion (999 mL/h) or slow infusion (333 mL/h). Study fluids will be used for resuscitation episodes (at rapid or slow infusion rates), dilution of compatible medications and maintenance solutions. Patients, health care providers and investigators will be blinded to the solutions being tested. The rate of bolus infusion will not be blinded.

Outcomes: The primary outcome is 90-day all-cause mortality. Secondary outcomes are: incidence of renal failure requiring renal replacement therapy within 90 days, incidence of acute kidney injury (Kidney Disease: Improving Global Outcomes stages 2 and 3), incidence of non-renal organ dysfunction assessed by Sepsis-related Organ Failure Assessment score at Days 3 and 7, and number of mechanical ventilation-free days within the first 28 days after randomisation.

Results and conclusions: The BaSICS trial will provide robust evidence on whether a balanced crystalloid, compared with saline, improves important patient outcomes in critically ill patients. BaSICS will also provide relevant information on whether bolus infusion rate affects outcomes in this population.

Trial registration: ClinicalTrials.gov NCT02875873.
collapse. A rapid fluid bolus may abruptly reduce the adrenergic tone and/or worsen myocardial compliance, leading to or aggravating haemodynamic instability. Despite increasing cardiac output, a fluid bolus (500 mL in 30 minutes) may decrease arterial elastance, compromising arterial blood pressure. In contrast, resuscitation protocols based on slower infusion rates and involving reduction of fluid infusion seem to be safe in specific populations of critically ill patients. Therefore, one crucial issue to be addressed is whether the fluid bolus infusion rate affects the outcomes of critically ill adult patients.

We describe a protocol for a multicentre, randomised, factorial, clinical trial that will assess the effects of Plasma-Lyte 148 versus saline as the fluid of choice in critically ill patients, as well as the effects of rapid and slow fluid challenge infusion rates on important patient outcomes.

Methods
Aims
We aim to determine whether a balanced crystalloid solution (Plasma-Lyte 148) used for fluid resuscitation reduces 90-day mortality compared with saline in critically ill patients. We also aim to determine the effect of rapid administration (999 mL/h) versus slow administration (333 mL/h) of crystalloid solution on 90-day mortality in critically ill patients at high risk of renal injury.

Study design and setting
The Balanced Solution versus Saline in Intensive Care Study (BaSICS) is a pragmatic, multicentre, 2 × 2 factorial, randomised controlled trial. Patients will be randomised to receive Plasma-Lyte 148 or saline, and to rapid (999 mL/h) or slow (333 mL/h) infusion rates.

Patients, health care providers and study investigators will be blinded to the solutions being tested but not to the rate of bolus infusion. Study fluids will be used for resuscitation episodes (at rapid or slow infusion rates). These same fluids will be used for dilution of compatible medications and maintenance fluids, but only patients who are determined to require fluid boluses (Table 1) will be enrolled. The primary outcome is 90-day mortality. We will recruit about 11,000 patients in at least 100 Brazilian ICUs (see Appendix 1, online at cicm.org.au/Resources/Publications/Journal). Patients will be enrolled after ICU admission.

Eligibility
Inclusion criteria
To be randomised, patients must meet all the following inclusion criteria:
• Need for fluid resuscitation or plasma expansion (Table 1), and the clinician considers that either Plasma-Lyte 148 or saline is equally appropriate for patients, with no specific indications or contraindications for any of the fluids or for rapid or slow infusion.
• Not expected to be discharged on the day after admission.
• At least one of the following risk factors for acute kidney injury:
  ➢ age ≥ 65 years
  ➢ hypotension (mean arterial pressure [MAP] < 65 mmHg or systolic blood pressure [SBP] < 90 mmHg) or use of vasopressors
  ➢ sepsis
  ➢ use of invasive mechanical ventilation or continuous non-invasive mechanical ventilation (including high-flow nasal cannula) for > 12 h
  ➢ oliguria (< 0.5 mL/kg/h for ≥ 3 h)
  ➢ serum creatinine level ≥ 1.2 mg/dL (women) or ≥ 1.4 mg/dL (men)
  ➢ liver cirrhosis or acute liver failure.

Exclusion criteria
We will apply the following exclusion criteria:
• age < 18 years

Table 1. Guidelines for volume expansion (fluid challenge) during the study period
These criteria suggest the need for volume expansion (item 1 plus item 2)
1. At least one sign of hypoperfusion:
   a. Heart rate > 120 beats/min
   b. SBP < 90 mmHg or MAP < 65 mmHg or decrease in SBP of > 40 mmHg from baseline
   c. Capillary refill time > 1 s
   d. Mottling score ≥ 2
   e. Lactate level > 2 mmol/L (> 18 mg/dL)
   f. ScvO₂ < 70%
   g. Urinary output < 0.5 mL/kg in past hour
2. At least one sign of responsiveness to fluid therapy or absence of signs of hypervolaemia:
   a. Pulse pressure variation > 13%
   b. Increase in pulse pressure > 5% after an expiratory pause of 15 s
   c. Passive leg elevation leads to increased cardiac index (> 10%) or pulse pressure (> 11%) or MAP (> 5%)
   d. Respiratory variation in CVP > 1 mmHg
   e. CVP ≤ 10 mmHg
   f. Absence of clinical signs of hypervolaemia when data for above symptoms not available

SBP = systolic blood pressure. MAP = mean arterial pressure. ScvO₂ = central venous oxygen saturation. CVP = central venous pressure.
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- acute renal failure treated with RRT or expected to require RRT within the next 6 hours
- severe electrolyte disturbance (serum sodium level ≤ 120 mmol/L or ≥ 160 mmol/L, serum potassium level ≥ 5.5 mmol/L)
- death considered imminent and inevitable within 24 hours
- patients with suspected or confirmed brain death
- patients receiving palliative care only
- patients previously enrolled in BaSICS.

Interventions

Patients will receive Plasma-Lyte 148 or saline during their ICU stay (limited to 90 days), by random assignment. When fluid expansion is indicated, it will be provided according to the randomisation group (rates of infusion of 999 mL/h or 333 mL/h) during the ICU stay (limited to 90 days) (Figure 1). Whenever possible, the assigned study fluid and rate should be adhered to during investigations and procedures performed while the patient is temporarily outside the ICU. The volumes and frequency of administration will be determined by the primary physician (Figure 2), but guidelines suggesting triggers for fluid infusion will be provided to the study centres (Table 1). Adherence to study fluids and infusion rate will be assessed on Days 1 to 3 after randomisation and on Day 7.

The study fluids will also be used when crystalloid solutions are indicated to maintain volume status. Infusion rates for maintenance solutions are at the discretion of health care providers. Medications and solutions with ingredients that are compatible with saline and Plasma-Lyte 148 (eg, sedative drugs, vasopressors and antibiotics) should be infused using the study fluids (Figure 2). A list of medications compatible with both study fluids will be sent to the participating centres (Appendix 2).

In some scenarios (eg, extreme electrolyte disturbances [Table 2]), study fluids should not be used; in these scenarios, the physician will be prompted to resume using study fluids as soon as the contraindication for the fluid no longer exists. In imminently life-threatening situations (Table 3), patients may receive rapid infusion boluses (999 mL/h) regardless of the infusion rate to which they have been randomly assigned.

We will suggest that investigators consider the late-strategy criteria of the AKIKI trial to indicate starting RRT (Table 4), because there is no consensus on whether early or late RRT is the most appropriate for critically ill patients. We will remind the centres that RRT should not be delayed if the late-strategy criteria in AKIKI are met.

Table 2. Specific situations in which the assigned study fluid must not be administered

<table>
<thead>
<tr>
<th>Situation</th>
<th>Recommended alternative fluid</th>
</tr>
</thead>
<tbody>
<tr>
<td>Severe hyperchloremia (chloride level ≥ 120 mmol/L)</td>
<td>Plasma-Lyte 148 or Ringer’s lactate</td>
</tr>
<tr>
<td>Severe hypernatremia (sodium level ≥ 160 mmol/L)</td>
<td>Plasma-Lyte 148 or Ringer’s lactate (if fluid resuscitation is needed)</td>
</tr>
<tr>
<td>Severe hyponatremia (sodium level ≤120 mmol/L)</td>
<td>Normal or hypertonic saline</td>
</tr>
<tr>
<td>Hyperkalaemia (potassium level ≥ 5.5 mmol/L)</td>
<td>Normal saline</td>
</tr>
</tbody>
</table>

CRF = case report form.
Outcomes

Outcomes are similar for both factors in BaSICS (saline versus Plasma-Lyte 148, and rapid versus slow infusion speed).

**Primary outcome**

The primary outcome is 90-day all-cause mortality.

**Secondary outcomes**

Secondary outcomes are:

- Renal failure requiring RRT within 90 days
- AKI (classified as Kidney Disease: Improving Global Outcomes [KDIGO] stage ≥ 2 at Days 3 and 7 after randomisation). For diagnosis of AKI, serum creatinine level and urine output will be assessed using the following criteria: twofold or higher increase in serum creatinine level from reference level, or urine output level < 0.5 mL/kg/h for ≥ 12 hours. The reference creatinine level will be the lowest of the randomisation creatinine and previous creatinine levels (the most recent value available in the previous 6 months and before current admission). If no previous creatinine value is available, it will be estimated using the Modification of Diet in Renal Disease equation:

\[
\text{Creatinine level} = 75/\left(186 \times (\text{age} - 0.203) \times F \times B\right) - 0.887
\]

in which \( F = 0.742 \) (female patients) and \( B = 1.21 \) (black patients). If a patient is classified as having a KDIGO score of 2 at randomisation, they will be excluded from the sample for the evaluation of this outcome.

- New respiratory, hepatic, cardiac, neurological and coagulation dysfunction, assessed by Sepsis-related Organ Failure Assessment scores at Days 3 and 7.\(^1\)
- Mechanical ventilation-free days at 28 days after randomisation.

**Tertiary outcomes**

Tertiary outcomes are:

- ICU and in-hospital mortality due to any cause
- Length of ICU stay
- Length of hospital stay.

**Other exploratory outcomes**

- Comparison of serum chloride levels between the four study groups over time.
- Quality of life (utility) assessment after 6 months, through the EuroQol five dimensions health state (EQ-5D) questionnaire, which will be administered to a selected subsample of about 1100 patients.

**Randomisation**

We will allocate patients in a 1:1:1:1 ratio to receive Plasma-Lyte 148 as slow infusion, Plasma-Lyte 148 as rapid infusion, saline as slow infusion or saline as rapid infusion. The randomisation list will be generated with online software using random permuted blocks, stratified by centre according to fluid type (A to F) and infusion speed. Therefore, each block will have 12 patients. Block size will not be disclosed to research personnel.

Research personnel will randomise patients via a web-based central, automated randomisation system, available 24 hours per day, maintained by the Research Institute HCor, São Paulo, Brazil. The assigned study group will only be disclosed after patients have been registered in the web-based randomisation system.

**Blinding**

Patients, health care providers, data collectors, outcome assessors and statisticians will be blinded to the study fluids (Plasma-Lyte 148 or saline). Plasma-Lyte 148 and saline will be macroscopically identical and will be available in identical plastic containers of 500 mL, identified with codes A, B, C, D, E and F. Blinding to fluid bolus infusion rate is not feasible. Thus, this intervention will remain open to those involved in patient care.
We will enrol 11 000 patients in the trial. We estimate that there will be a mortality rate of 35% within 90 days in the control groups (saline or rapid infusion), based on the eligibility criteria applied to the databases of two Brazilian multicentre studies. The study will have a statistical power of 89% to detect a hazard ratio of 0.90 or less for 90-day mortality, with an alpha level of 0.05.

We do not expect a significant interaction between the two interventions (Plasma-Lyte 148 versus saline and slow versus rapid infusion rate). Nevertheless, if such interaction exists, the study will have a power of 80% to detect a positive hazard ratio of 0.835, considering that Plasma-Lyte 148 and slow infusion speed will result in lower mortality.

Statistical analysis
We will prepare a detailed statistical analysis plan before patient enrolment begins, which is intended to be published or made available electronically. All analysis will be conducted on the intention-to-treat principle. The effect of type of fluid (Plasma-Lyte 148 v saline) and the infusion rate (rapid v slow infusion) on the primary outcome will be assessed with Cox proportional hazards regression and Kaplan–Meier curves, and will be presented as hazard ratios with 95% confidence intervals and P values. Binary secondary outcomes will be compared using χ² tests and presented as risk ratios with 95% CI and P values. Results for continuous outcomes will be expressed as mean differences, 95% CIs and P values, calculated with the independent t test, or Wilcoxon rank sum test in the case of non-normal distribution. We will analyse the available dataset for secondary and tertiary outcomes.

Subgroup analysis
The effect of the type of fluid (Plasma-Lyte 148 v saline) and infusion speed on the primary outcome will be assessed using Cox proportional hazards regression in the subgroups of patients with and without the following characteristics at baseline:
- sepsis
- AKI KDIGO Stage 1
- admitted from the surgical block
- traumatic brain injury
- APACHE II score ≥ 25
- patients receiving > 1.0 L of saline in the 24 hours before randomisation.

We will infer a subgroup effect if the P value for homogeneity of treatment effects is < 0.05.

As exploratory analysis, we will assess the subgroup of patients who received at least 6 L of fluid in the first 3 days after ICU admission. We will also perform a dose-response analysis to assess whether there is a minimum volume to be infused to obtain a positive association between balanced solution used and outcome. This analysis is sustained by previous research suggesting that the potential benefit from balanced solutions may only occur in aggressively resuscitated patients, but will be considered strictly exploratory.

Interim analyses and data monitoring committee
We have set up a data monitoring committee (DMC) with the primary aim of helping to ensure the safety of patients in the trial by protecting them from avoidable harm. A group of independent experts has been appointed to the DMC: Gordon Guyatt (Chair), methodologist and triallist; Niall Ferguson, triallist and intensivist; and Stephen Walter, statistician. All have extensive experience in trial methodology.
The DMC will initially prepare a charter specifying details of the committee, its operation, meeting schedule and the trial stopping rules. The rules will be based on the principles listed below. We will conduct interim analyses after recruitment of about 25%, 50% and 75% of the study cohort. Based on the interim analyses and occasionally on external evidence, the DMC will decide whether there is evidence beyond reasonable doubt to support that the experimental treatment (Plasma-Lyte 148 v saline, and slow v rapid infusion rate) increases 90-day mortality, with \( P < 0.01 \). The members of the DMC may consider requesting to continue the study for an additional 3 months to confirm such effects (especially if \( P \) is between 0.01 and 0.001). If the safety criterion is met in one of the factors analysed in the study, the corresponding factorial arm will be stopped and the study will continue with the remaining one.

In the case of evidence of superiority of Plasma-Lyte 148 over saline, or of slow infusion over rapid infusion, with \( P < 0.001 \) in the interim analysis conducted after the recruitment of 50% or more patients, the DMC may also consider stopping the study. However, the DMC will request to continue the study for an additional 3 months and for the analyses to be repeated to confirm the difference between the treatments and to allow stabilisation of estimated effect. In accordance with the DMC, we decided that the study will not be discontinued because of a benefit in the first interim analysis (after the recruitment of 25% of the sample). The reasons for this decision were:

- Early discontinuation of randomised trials because of a benefit tends to produce biased estimates of effect (overestimation of the true effect), which may lead to erroneous medical guidelines and decisions, especially with a small number of events.\(^{20}\)
- According to the ethical principle of non-maleficence, a new treatment should not be used until there is clear, objective evidence that it is beneficial.
- Clinical practice does not usually change unless there is convincing evidence of the advantages of the new treatment, which will be undermined if the study is discontinued early due to a benefit.\(^{21}\)

**Recruitment strategy**

Recruiting 11 000 critically ill patients is clearly challenging. We anticipate that we should recruit this sample size within 48 months in 100 ICUs. We will use several strategies to ensure adequate recruitment:

- Submission to all ethics committees will be supported by staff at the Research Institute HCor, with the aim of shortening time to study approval.
- Adequate training will be provided to sites in investigator meetings and during site initiation visits.
- Study procedures will be kept as simple as possible and we will foster a culture of embedding study activities in the routines of participating ICUs.
- Sites will receive study fluids and reimbursement for patient inclusion.
- Investigators will be acknowledged in all publications and will be offered the opportunity to lead substudies.
- We will prioritise promotion of patients’ enrolment using several strategies (phone contacts, emails, newsletters, weekly enrolment reports and others) in the daily activities of the Research Institute HCor.
- We will act according to the 12 components for marketing clinical trials proposed by Francis and colleagues.\(^{22}\)

**Trial organisation and funding**

The Research Institute HCor is the sponsor and coordinator of the study, in association with the Brazilian Research in Intensive Care Network (BRICNet). The trial structure includes the following groups: the coordinating centres, investigators, steering committee and DMC.

The study will be conducted as part of and funded by the Program to Support Institutional Development of the Universal Health System from the Brazilian Ministry of Health. Baxter Latin America will provide the fluids and transport logistics used in the trial. Baxter will not be involved in any aspects of trial design, execution, analysis or interpretation of the results.

**Safety**

All unexpected serious adverse events related to the study interventions must be reported to the Research Institute HCor within 24 hours. An unexpected serious adverse event directly related to the study is defined as any event meeting these two criteria:

- Any fatal or life-threatening event (immediate risk of death), or any event that causes sequelae or permanent disability, or that extends hospitalisation.
- The attending physician believes the event is related to the patient’s inclusion in the BaSICS trial.

Serious adverse events will be considered as “related to the study” if the attending physician believes that the event was probably caused by the fluid and/or the rate of infusion used in the study and follows a plausible time sequence after the administration of the fluid.

**Ethics and dissemination**

**Ethics approval and registration**

This study protocol, version 1.5, from August 2016, has been approved by the Research Ethics Committee of the Coordinating Centre (Hospital do Coração/Associação do Sanatório Sírio) (CAAE: 57395816.6.1001.0060). The study will not begin at the participating centres until approval has been obtained from the responsible local ethics committee for each participating ICU. All amendments to the protocol must be approved by the internal review board.
board of each participating centre. This protocol conforms to the Standard Protocol Items: Recommendations for Interventional Trials recommendations, and has been registered in ClinicalTrials.gov (NCT02875873).

Informed consent
Whenever possible, prospective written informed consent will be requested before randomisation from all eligible patients, or from their legal representatives when the patients are unable to provide consent due to communication or cognitive limitations. If no legal representative is available at the time, the patient will be randomised, and written consent from the patient or legal representative will be sought as soon as possible afterwards (deferred consent).

Confidentiality
Each patient and research centre will be identified by a unique number in the electronic case report form. Information obtained from medical records must be handled as confidential data by the research centres; it must be kept in restricted access locations, and anonymity must be ensured on interim and final reports.

Data sharing
We intend to make the study database available to other researchers. In the first 2 years after the publication of the main manuscript, the investigators will perform analyses for substudies proposed by investigators from the BaSICS collaborative group. In this phase, the database will be kept in conditions of restricted access by the study coordinators, and third parties will have access to it only with previous authorisation of the BaSICS steering committee, which will analyse each research proposal and statistical analysis plan. The steering committee will provide the requested data if the proposal does not conflict with future or ongoing substudies of investigators from the collaborative group. After 2 years, all data collected during the BaSICS trial will be publicly available on a free-access platform. We emphasise that specific data that may identify a patient, such as initials or date of birth, will not be made publicly available. Each individual requesting access to the database must formally commit to notifying the steering committee of the study in the event that any database information identifying a patient is found.

An individual patient data meta-analysis grouping the data from this study and the Plasma-Lyte 148 versus Saline Study (NCT02721654) is planned.

Dissemination
The BaSICS steering committee will publish the study findings, whatever they are. The main manuscript will be submitted by the writing committee on behalf of the research group (BaSICS investigators and the BRICNet). The names of other trial committees and all collaborators will be listed after the text.

Conclusions
The BaSICS trial will provide robust evidence as to whether the use of a balanced crystalloid fluid reduces 90-day mortality compared with saline in critically ill patients receiving fluid resuscitation. BaSICS will also provide relevant information on whether the fluid bolus infusion rate affects outcomes in this population of patients.

Competing interests
We declare that Baxter Latin America will donate fluids and provide distribution logistics for the BaSICS trial. Baxter will not be involved in any aspect of the study design, analysis or decision to publish the results. Luciano Azevedo and Murillo de Assunção received personal grants for the advisory board from Baxter Brazil. Otavio Berwanger has received research grants for investigator-initiated clinical trials from AstraZeneca, Amgen, Boehringer-Ingelheim, Roche and Bayer, which are unrelated to the topic of this study.

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