

A protocol for the 0.9% saline versus Plasma-Lyte 148 for intensive care fluid therapy (SPLIT) study

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The administration of intravenous (IV) fluid is a common therapy in acutely unwell patients. Globally, the choice of which fluid to use for resuscitation is influenced by geography.¹ Crystalloid use is proportionally higher in New Zealand intensive care units than in other parts of the world.¹ Although recent data support the use of crystalloids rather than colloids in ICU patients,² the most appropriate crystalloid fluid to use in critically ill patients is uncertain. While 0.9% saline is the most commonly administered IV fluid in the world, preclinical and early clinical data suggest that it may give rise to a range of adverse effects.³⁻¹⁰ These include immune dysfunction,⁷ increased blood transfusion needs,⁴ gastrointestinal dysfunction,^{9,10} decreased renal cortical perfusion and impairment of renal function.⁸ An alternative to using 0.9% saline (which contains about 1.5 times as much chloride as normal plasma) is to use a buffered crystalloid solution with an electrolyte composition that more closely resembles that of plasma.¹¹

A recent, retrospective, observational study of patients with sepsis treated with vasopressors and crystalloids showed that resuscitation with buffered fluids was associated with a lower risk of in-hospital mortality than resuscitation with 0.9% saline, and that mortality risk progressively decreased as patients received larger proportions of buffered fluids.³ In a single-centre, prospective, open-label, sequential-period, pilot study of 1533 critically ill patients, the implementation of a chloride-restrictive fluid strategy, which included a change from using 0.9% saline to using buffered crystalloid solutions, was associated with a significant decrease in needs for renal replacement therapy (RRT) and a decrease in the risk of developing acute kidney injury (AKI).⁵ Similarly, a large retrospective study of adults undergoing major open abdominal surgery suggested that, compared with 0.9% saline, the use of Plasma-Lyte (Baxter Healthcare), which is a buffered crystalloid solution, was associated with a decreased risk of major complications including renal failure needing dialysis.⁴ The biological plausibility that 0.9% saline might cause AKI is supported by magnetic resonance imaging in healthy adults showing that there is a significant reduction of renal artery blood flow velocity and renal cortical tissue perfusion in response to infusion of 0.9% saline, but not after infusion of Plasma-Lyte 148.⁸

No large-scale interventional trial has compared the use of 0.9% saline with a buffered crystalloid solution. Plasma-

ABSTRACT

Background: 0.9% saline is the most commonly used intravenous (IV) fluid in the world. However, recent data raise the possibility that, compared with buffered crystalloid fluids such as Plasma-Lyte 148, the administration of 0.9% saline to intensive care unit patients might increase their risk of acute kidney injury (AKI).

Objective: To describe the protocol for the 0.9% Saline v Plasma-Lyte 148 for ICU Fluid Therapy (SPLIT) study.

Methods: This is a multicentre, cluster-randomised, double crossover feasibility study to be conducted in four New Zealand tertiary ICUs over a 28-week period and will enrol about 2300 participants. All ICU patients who need crystalloid IV fluid therapy (except those with established renal failure needing dialysis and those admitted to the ICU for palliative care) will be enrolled. Participating ICUs will be randomly assigned to 0.9% saline or Plasma-Lyte 148 as the routine crystalloid IV fluid, in a blinded fashion, in four alternating 7-week blocks.

Main outcome measures: The primary outcome will be the proportion of patients who develop AKI in the ICU. Secondary outcomes will include the difference between the most recent serum creatinine level measured before study enrolment and the peak serum creatinine level in the ICU; use of renal replacement therapy; and ICU and in-hospital mortality. All analyses will be conducted on an intention-to-treat basis.

Results and conclusion: The SPLIT study started on 1 April 2014 and will provide preliminary data on the comparative effectiveness of using 0.9% saline v Plasma-Lyte 148 as the routine IV fluid therapy in ICU patients.

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Lyte 148 is the logical comparator to 0.9% saline for a large-scale crystalloid trial because, unlike other commercially available low-chloride crystalloid fluids such as Hartmann's solution, it does not contain calcium and is therefore compatible with blood products preserved in citrate-based solutions. Plasma-Lyte 148 contains acetate, which is metabolised by the liver to bicarbonate and produces a near-physiological solution. The electrolyte com-

Table 1. Electrolyte concentrations in human plasma, 0.9% saline and Plasma-Lyte 148

Electrolyte (mmol/L)	Plasma	0.9% Saline	Plasma-Lyte 148
Sodium	140	150	140
Potassium	5	0	5
Chloride	100	150	98
Calcium	2.2	0	0
Magnesium	1	0	1.5
Bicarbonate	24	0	0
Acetate	0	0	27
Gluconate	0	0	23

Table 2. Double crossover design for the SPLIT study

ICU site	1st 7 weeks	2nd 7 weeks	3rd 7 weeks	4th 7 weeks
	Fluid	Fluid	Fluid	Fluid
1	A	B	A	B
2	B	A	B	A
3	A	B	A	B
4	B	A	B	A

SPLIT = 0.9% Saline v Plasma-Lyte 148 for Intensive Care Unit Fluid Therapy.

positions of Plasma-Lyte 148 and 0.9% saline are shown in Table 1.¹¹ Here we outline the protocol for the 0.9% Saline v Plasma-Lyte 148 for ICU Fluid Therapy (SPLIT) study.

Design and objectives

The SPLIT study is a prospective, multicentre, randomised, double-blind, cluster, double crossover feasibility study comparing the administration of 0.9% saline with Plasma-Lyte 148 as the routine IV crystalloid fluid therapy in ICU patients. We will recruit patients from four tertiary ICUs in New Zealand (the Auckland Hospital Cardiac and Vascular ICU and Department of Critical Care Medicine, and the ICUs of Christchurch Hospital and Wellington Hospital) over a 28-week period. The cluster, double crossover design means that the participating ICUs, rather than individual patients, will be randomly assigned to use the study IV fluids. All researchers will be blinded to which fluid they are using. Two ICUs will initially use 0.9% saline as the routine IV fluid, and the other two ICUs will use Plasma-Lyte. After a 7-week period, the ICUs will change to the opposite IV fluid (Table 2). Further crossovers occur so that each ICU will ultimately use each study fluid twice as the routine IV fluid. Patients who remain in the ICU through one or more crossover periods will continue to use the fluid to which they were originally assigned for 90 days. As a result, no

Table 3. Primary and secondary outcomes and proposed subgroup analyses for the SPLIT study

Primary outcome

- Proportion of patients with AKI or renal failure, based on creatinine levels,* by RIFLE criteria

Secondary outcomes

- Delta creatinine[†]
- Cumulative incidence of AKI, based on creatinine levels, by RIFLE criteria
- Cumulative incidence of AKI, based on creatinine levels, by KDIGO category and AKI stages 1–3
- Proportion of patients needing RRT during ICU stay
- Proportion of patients needing RRT after hospital discharge (among patients who needed RRT in the ICU)
- Proportion of patients needing mechanical ventilation
- Duration of mechanical ventilation
- Length of ICU admission from the time of SPLIT enrolment
- Length of hospital admission from the time of SPLIT enrolment

Predefined subgroups

- Patient with sepsis (APACHE III codes 501, 502, 503, 504)
- Patients with trauma (APACHE III codes 601, 602, 603, 604, 605)
- Patients with traumatic brain injury (APACHE III code 601)
- Patients with an APACHE II score of ≥ 25
- Patients admitted to the ICU after cardiac surgery (APACHE III codes 1206, 1207, 1208, 1209, 1212)

SPLIT = 0.9% Saline v Plasma-Lyte 148 for Intensive Care Unit Fluid Therapy. AKI = acute kidney injury. RIFLE = risk, injury, failure, loss, end-stage renal failure. KDIGO = kidney disease: improving global outcomes. RRT = renal replacement therapy. ICU = intensive care unit. APACHE = Acute Physiology and Chronic Health Evaluation. * Highest value measured during patient's stay in the ICU (censored at Day 90). † Difference between the pre-enrolment creatinine and the peak creatinine levels measured during the ICU stay (censored at Day 90).

washout period between crossovers is needed. Because of the study design, the sample size is not fixed. Instead, the sample size will be determined by the number of patients admitted to the study ICUs during the 28 weeks of recruitment who are eligible for enrolment. Based on expected admission rates, we expect that about 2300 patients will be enrolled over the 28 weeks of the study.

The objective of our study is to provide preliminary data on the comparative effectiveness of 0.9% saline v Plasma-Lyte 148 as the routine IV fluid therapy in ICU patients. Table 3 shows a summary of the primary and secondary outcomes and the predefined subgroup analyses. We will follow up patients until hospital discharge, with censoring applied at death, or at Day 90 (2160 hours) from study enrolment for patients with an extended hospital stay. All patients who need RRT will be followed up for 3 months to establish if they have end-stage renal failure, according to the risk, injury, failure, loss and end-stage (RIFLE) criteria.¹²

The primary outcome will be the proportion of patients with either AKI or renal failure, according to RIFLE criteria

Table 4. RIFLE categories and KDIGO AKI criteria

Kidney injury classification	Criteria
Risk	1.5–1.9 × increase from baseline Cr*
Injury	2–2.9 × increase from baseline Cr*
Failure	≥ 3 × increase from baseline Cr,* or increase in serum Cr to ≥ 350 µmol/L with a rise of ≥ 44 µmol/L
Loss	Persistent loss of kidney function for > 4 weeks
End-stage	Dialysis-dependent for > 3 months
KDIGO Stage 1	1.5–1.9 × increase from baseline Cr,* or ≥ 26.5 µmol/L increase in serum Cr
KDIGO Stage 2	2–2.9 × increase from baseline Cr*
KDIGO Stage 3	≥ 3 × increase from baseline Cr,* or increase in serum Cr to ≥ 353.6 µmol/L, or start of RRT

RIFLE = risk, injury, failure, loss, end-stage renal failure. KDIGO = kidney disease: improving global outcomes. AKI = acute kidney injury. Cr = creatinine. ICU = intensive care unit. RRT = renal replacement therapy. * During ICU admission.

and based on serum creatinine levels (Table 4).¹² For the purposes of the RIFLE criteria,¹² we will record the baseline creatinine level as the lowest serum creatinine in the hospital laboratory records for the 6 months before the current ICU admission. The peak creatinine will be defined as the highest serum creatinine during the ICU admission.

Secondary outcomes will be the Δ creatinine (the difference between serum creatinine level measured immediately before study enrolment and peak creatinine level in the ICU); the cumulative incidence of AKI by category, based on the RIFLE classification;¹² the cumulative incidence of AKI, by KDIGO criteria (Table 4);¹³ the need for RRT during the ICU stay and after hospital discharge; the proportion of patients

Table 5. Inclusion and exclusion criteria for the SPLIT study

Inclusion criteria:

- patient must be in the ICU and need crystalloid fluid therapy

Exclusion criteria include patients who:

- are currently receiving or expected to need RRT within 6 hours of ICU admission
- are usually on dialysis for end-stage renal failure
- were admitted to the ICU solely for consideration of organ donation or for palliative care
- were previously enrolled in the SPLIT study

SPLIT = 0.9% Saline v Plasma-Lyte 148 for Intensive Care Unit Fluid Therapy. ICU = intensive care unit. RRT = renal replacement therapy.

needing mechanical ventilation (MV) and the MV duration; the ICU and hospital lengths of stay; and ICU and in-hospital mortality. We will also collect data on the proportion of patients who need ICU readmission within their index hospital admission.

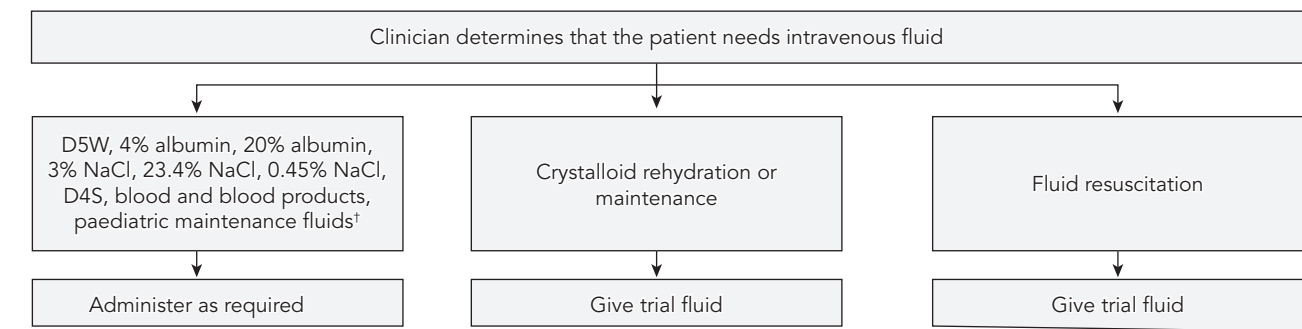
Participants

All ICU patients needing crystalloid fluid therapy will be eligible to be included in this study. The major exclusion criteria relate to pre-existing end-stage kidney disease needing dialysis, imminent need for RRT at ICU admission, and previous SPLIT study enrolment. Table 5 lists the full eligibility criteria.

Treatments

Eligible patients needing IV fluid therapy will receive masked study fluid with the rate, duration, and frequency of administration determined by the treated clinician (Figure 1). As much as possible, crystalloid treatment during investigations and procedures performed outside the ICU will be

Figure 1. Fluid administration during the SPLIT study



SPLIT = 0.9% Saline v Plasma-Lyte 148 for Intensive Care Unit Fluid Therapy. D5W = 5% dextrose in water. D4S = 4% dextrose and 0.18% saline. † 10% dextrose + 72 mmol/L NaCl in 500 mL + 20 mmol/L KCl (for children < 6 months), 5% dextrose + 72 mmol/L NaCl + 20 mmol/L KCl (for children 6 months to 5 years), or 2.5% dextrose + 36 mmol/L NaCl + 10–20 mmol/L KCl (for children > 5–16 years).

Figure 2. Masked study fluids A and B

with the assigned study fluid. Open-label study fluids will be available for use in rare situations when the treating clinician believes that there is a specific indication for either 0.9% saline or Plasma-Lyte 148, eg, for acute brain injury, when the higher sodium content of 0.9% saline may make it advantageous because it may decrease the risk of cerebral oedema.¹⁴ Concomitant treatment with non-study specialised crystalloid solutions, colloids and blood products will be at the discretion of the treating clinician.

The allocation of study treatments in each cluster will be determined ahead of time by the study statistician. Masked study fluids appropriate for each study block will be manufactured in a blinded fashion, labelled Fluid A or Fluid B, in indistinguishable 1000 mL bags (Figure 2). The allocation will be known only to the manufacturer of the fluid and two members of the administrative staff at the coordinating centre, who will not be otherwise involved in the study. Allocation concealment will be maintained until all analyses (including any post-hoc analyses) are complete. Because the study allows for the per-protocol use of open-label 0.9% saline or Plasma-Lyte 148, there are no situations in which it

Table 6. Data to be collected in the SPLIT study

Baseline data

- Age, sex, ethnicity
- ICU admission source
- Baseline APACHE II score
- APACHE III diagnostic code
- Baseline creatinine level (lowest pre-illness creatinine level in the 6 months before ICU admission)
- Pre-enrolment creatinine level
- Comorbidities (chronic respiratory disease, chronic cardiovascular disease, leukaemia, myeloma, immunosuppression by disease or therapy, hepatic failure, cirrhosis, lymphoma, AIDS or metastatic cancer)
- Mechanical ventilation at enrolment
- IV fluids* in the 24 hours before enrolment

Daily data

- IV fluids* received, Day 0 to Day 3 (inclusive)
- Highest creatinine level recorded in the ICU, Day 0 to Day 7

Hospital discharge and Day 90 follow-up data

- Total amount of study fluid, open-label Plasma-Lyte 148 or open-label 0.9 % saline received in the ICU until Day 90
- Highest creatinine level in the ICU (censored at Day 90)
- Duration of mechanical ventilation
- Need and indication for RRT
- Need for RRT after hospital discharge among patients who needed RRT in the ICU
- ICU length-of-stay from enrolment
- Hospital length-of-stay from enrolment
- Vital status (alive or dead) at ICU and hospital discharge

SPLIT = 0.9% Saline v Plasma-Lyte 148 for Intensive Care Unit Fluid Therapy. ICU = intensive care unit. APACHE = Acute Physiology and Chronic Health Evaluation. AIDS = acquired immune deficiency syndrome. IV = intravenous. RRT = renal replacement therapy. * Type and amount, including crystalloid fluids (Plasma-Lyte 148, 0.9% saline, 5% dextrose, paediatric maintenance fluid and other crystalloids); colloids (4% albumin, 20% albumin, gelifusine, voluven/volulyte and other colloids); and blood products (packed red blood cells, fresh frozen plasma, platelets and cryoprecipitate).

is envisaged that unblinding of treatment interventions will be needed. Because revealing treatment allocation of a single patient would unblind an entire cluster, all requests to unblind a treatment will be directed to the independent data safety monitoring board (DSMB). If the DSMB determines that, for patient safety reasons, unblinding of study fluid is needed, systems are in place for this to occur.

Ethical issues

Our study will compare the effectiveness of two established treatments which are both commonly administered to ICU patients in usual clinical practice in these study ICUs.¹⁵ All the study data are already being collected for clinical and/or quality assurance purposes. The study has been granted ethics approval by the New Zealand Northern B Ethics Health and Disability Committee (12/NTB/57) on the basis

of the provision of information to patients and/or their next of kin and the opportunity for them to opt out of the use of their data if they wish. Our trial has been registered on the Australian and New Zealand Clinical Trials Registry (ACTRN 12613001370796).

Data collection and management

Data will be collected in each centre by trained research coordinators and entered into a web-based case report form (see Table 6 for details of the data to be collected). Baseline data will include ICU admission source, Acute Physiology and Chronic Health Evaluation (APACHE) II score, APACHE III diagnostic code, and underlying medical comorbidities. Requirements for MV at the time of enrolment and details of IV fluids administered in the 24 hours before enrolment will also be collected. During the ICU stay, daily data will include the volumes of specific IV fluids and blood products administered to patients from Day 0 (the day of study enrolment) to Day 3 (inclusive). When the creatinine level is measured as part of routine clinical care, the highest daily level will be recorded from Day 0 to Day 7. The need for RRT in the ICU will be assessed daily and, for patients who receive RRT in ICU, the indications for starting RRT as well as any need for RRT after hospital discharge will be recorded. Prespecified indications for RRT will be clinically significant oliguria; serum potassium >6.5 mmol/L; arterial or venous pH <7.2 ; serum urea >25 mmol/L; serum creatinine >300 mmol/L; organ oedema; other renal failure-related indications; and other non-renal failure-related indications. All indications for RRT that are present immediately before commencement of RRT will be recorded on the case report form. In addition to renal failure-related data points, the duration of MV, length of ICU and hospital stays from time of SPLIT study enrolment, and in-hospital mortality data will be recorded.

A web-based screening log will capture the details of patients who are eligible but not enrolled in the study as well as the number of patients excluded and the reasons for exclusion. The study website includes features for automatic checking of the internal consistency of data and needs manual verification of values which are outside specified expected ranges. A range of website reporting functions will allow for remote monitoring of study data by monitoring staff at the coordinating centre.

Medication and logistics

All study fluid will be manufactured and masked by Baxter Healthcare and stored at a central location in Auckland and distributed to study sites as needed. During the crossover periods, each ICU will ensure that patients continue to receive the study fluid (Fluid A or Fluid B) to which they were originally assigned.

Sample size and power

Due to the current lack of established statistical methodologies for calculating sample size for cluster randomised, double crossover trials with binary outcome variables, we have not performed any sample size calculations. However, data obtained in our study may be used to model the sample size needs for a larger study of 0.9% saline v Plasma-Lyte 148 for ICU fluid therapy using this design.

Statistical analysis

We will conduct analyses on an intention-to-treat basis. Statisticians at the Australian and New Zealand Research Centre, Melbourne, Australia, will perform the data analyses. Primary and secondary outcomes will be analysed at an individual patient level using hierarchical longitudinal analysis techniques, accounting for the attending hospital and fluid sequence, with patients nested within sites and sites crossing over (not patients). Binomial outcomes will be assessed using generalised estimating equations with results reported as odds ratios and 95% confidence intervals. Continuous outcomes will be analysed using generalised linear modelling and reported as differences and 95% CIs or ratios and 95% CIs, as appropriate.

We will perform additional analyses adjusting for an a priori defined list of covariates (the presence or absence of trauma, APACHE III admission diagnosis, age, ICU admission source, APACHE II score, and baseline serum creatinine level) with results reported overall and at the individual ICU level. Subgroup analyses will be performed on the prespecified subgroups of interest listed in Table 3. In the primary analysis, no assumptions will be made for missing values and, when baseline or peak creatinine levels are not available, we will perform a complete case analysis. However, we will undertake sensitivity analyses to account for extreme scenarios for missing values. All analyses will be performed using SAS version 9.3 (SAS Institute) and a two-sided P of 0.05 will be considered to be statistically significant. As the principal aim of our study is to provide preliminary data and determine feasibility, no adjustment for multiple comparisons will be made. All analyses will be conducted in accordance with a prespecified statistical analysis plan which will be published before the study database is locked or any analyses are undertaken.

Data safety monitoring

A committee of independent experts has been appointed to the DSMB: Anders Perner (chair), Andrew Forbes (statistician), and John Morgan. The responsibilities of the DSMB are outlined in a charter prepared by the SPLIT management committee and signed by all members of the DSMB. The DSMB will undertake general safety monitoring and make

recommendations to the management committee when they judge that the ethical conduct of the study or its scientific integrity may be jeopardised. The DSMB will also review summaries of adverse events. Given the existing knowledge and current widespread use of the IV fluids being tested, it is not anticipated that the DSMB will make recommendations to stop the trial early on the basis of reported adverse events known or suspected to be due to either IV fluid.

Funding and support

Our study is an investigator-initiated study endorsed by the Australian and New Zealand Intensive Care Society Clinical Trials Group and primarily funded by a research partnership grant from the Health Research Council of New Zealand. In addition, Baxter Healthcare is manufacturing and providing masked study fluid and a grant to support the study. Baxter Healthcare had no role in the development of the study protocol and all study analyses will be conducted independently of the funding organisations.

Summary

The SPLIT study is a randomised double-blind, cluster, double crossover study comparing the administration of 0.9% saline with Plasma-Lyte 148 as the routine IV crystalloid fluid therapy in ICU patients. There are sufficient early clinical data and biological plausibility to support the hypothesis that using Plasma-Lyte 148 instead of 0.9% saline for IV fluid therapy will decrease the risk of developing AKI. Our study is part of a research program that will determine the relative efficacy and safety of using 0.9% saline v Plasma-Lyte 148 for IV fluid therapy in ICU patients.

Competing interests

From Baxter Healthcare, JM, RB, SH, SG and PY received honoraria of <US\$5000 for consulting, the Medical Research Institute of New Zealand received a research grant of US\$149935, and 0.9% saline 10000L and Plasma-Lyte 148 10000L were provided for the study.

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