CLINICAL TRIAL PROTOCOL

FLUid intervention and **R**enal **O**utcome **Trial** in patients undergoing major surgery: an observational single-centred study

(FLURO Trial)

A single-centred prospective observational study investigating the effects of intravenous fluids on renal injury in adult patients undergoing major surgery

Protocol Version: Version 2
Date 31st March 2014

GENERAL INFORMATION

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1.3 Coordinating Department

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STUDY SYNOPSIS

Title:	Fluid intervention and Renal Outcome Trial in patients undergoing major surgery: an observational single-centred study (FLURO Trial).
Short Title:	Fluid therapy in major surgery.
Design:	Single-centred, prospective observational study. Information about intravenous fluid intervention (type of fluid and amount) for adult patients undergoing major surgery (duration >2 hours and at least one overnight stay) will be collected over a 6-week period. The effects of these fluids on renal function will be investigated.
Study Centers:	1
Hospital:	Austin Hospital
Study question:	What are the association between perioperative intravenous fluids and renal function in adult patients undergoing major surgery at a University teaching hospital.
Study Objectives:	To determine the association between perioperative intravenous fluids and renal function in adult patients undergoing major surgery.
Primary Outcome:	Acute kidney injury (AKI), defined by an increase in creatinine greater than 25% or 0.5 mg/dL (44 µmol/L) from baseline to peak value within the first 72-hours postoperatively.
Secondary Outcomes:	Serum electrolytes Acid base disturbances Post-operative complications Requirements for ICU Requirement for dialysis or hemofiltration Duration of ICU stay Hospital length of stay In-hospital mortality
Inclusion criteria:	Adult patients ≥ 18 years Elective or emergency surgery Surgery duration > 2 hours Requiring at least one overnight stay
Exclusion criterion:	<18 years in age Liver transplantation
Number of planned Subjects:	400-600

Investigational product:	Nil
Safety considerations:	**This is an observational study only. There is no departure from standard care at any stage. It only involves the collection of data that has already been collected for clinical or quality assurance purposes.** Perioperative care and fluid intervention will remain completely at the discretion of the treating clinicians.
Statistical Methods:	Primary analyses: will be unadjusted analyses in which binary outcomes will be compared using relative risks with 95% confidence intervals and chi square tests and continuous outcomes will be compared with the use of mean differences and un-paired T-tests assuming that normality assumptions are meet. A complete description of the statistical analyses will be specified in a statistical analyses plan, finalised prior to completion of all data collection. If normality assumptions data transformation will be attempted, such as a logarithm transformation, and if this fails to proceed to a Mann-Whitney rank based test. Adjusted analyses: will be performed using Poisson regression for binary outcomes and linear regression for continuous outcomes. Baseline covariates will include age, gender, elective vs. emergency surgery, surgical specialty of admission, type of operation, and baseline serum creatinine level. Multivariable models will be developed to study the predictors of AKI and the independent association between fluid choice and renal outcomes.
Subgroups:	Patients undergoing abdominal surgery Patients undergoing vascular surgery Patients undergoing thoracic surgery Patients undergoing other major surgeries (orthopaedics, urology etc.) Patients undergoing emergency surgery.

ABBREVIATIONS

IV	Intravenous
CPB	Cardiopulmonary bypass
ECGs	Electrocardiographs
ICU	Intensive Care Unit
APACHE	Acute Physiology and Chronic Health Evaluation

LAY SUMMARY

The administration of intravenous (IV) crystalloid fluids (also known as fluid therapy) is a ubiquitous intervention in patients undergoing surgery. Worldwide, the most commonly used crystalloid fluids available for patients undergoing major surgery include Saline (0.9%), Hartmann's and Plasmalyte solutions. All three solutions are available for IV use at Austin Hospital and considered standard of care for all patients undergoing major surgery. Choice of these fluids amongst anaesthetists at Austin Hospital is similar to worldwide practices. In this study we will be collecting information about intravenous fluid intervention (type of fluid and amount) for adult patients undergoing major surgery (duration >2 hours and at least one overnight stay). Data will be collected over a 12-week period. Specifically, the effects of these fluids on kidney function will be investigated. Perioperative care and fluid intervention therefore will remain completely at the discretion of the treating clinicians.

As this is an observational study, there is no departure from standard care at any stage. It involves the collection of data that has already been collected for clinical or quality assurance purposes.

Whilst the main focus of the study is to investigate the association between these fluids and kidney function, important secondary endpoints that we will collect include changes in electrolytes, post-operative complications, requirements for ICU, requirement for dialysis or hemofiltration, hospital length of stay, and in hospital mortality. All data will be collected from medical records. This study will establish the preliminary evidence base for the design of a larger blinded interventional study (The SPLIT Study, HREC/12/Austin/161), which has been submitted to the Austin Research Ethics Unit and is currently being considered for approval.

The current study will inform clinicians looking after patients undergoing major surgery about the association between these fluids with renal injury.

This study will be also be used in Fulfilment of University of Melbourne BSc Honours Project for Ms Angelica Armellini.

1.4 Fluid therapy in patients receiving major surgery

The administration of intravenous (IV) crystalloid fluid (also known as fluid therapy) is a ubiquitous intervention in patients undergoing surgery. Worldwide, the most commonly used crystalloid fluids available for patients undergoing major surgery

include Saline (0.9%), Hartmann's and Plasmalyte solutions. Choice of fluid therapy is based frequently dependent on geography[1], and choice of fluid amongst anaesthetists at Austin Hospital is similar to worldwide practices.

1.5 Saline (0.9%) vs. Plasmalyte vs. Hartmann's solution

Saline has been used in clinical practice for fluid therapy since the late 1800s. While it is the most commonly used IV fluid in the world[1] recent data raise the possibility that it might increase the risk of developing kidney damage in acutely unwell patients compared to fluids with lower concentrations of chloride such as Plasmalyte[2]. While this increased risk of kidney damage with the use of saline is plausible[3], current data are insufficient to recommend clinical practice change[4] and data from an interventional trial are urgently needed. However, the design of such a Trial requires sufficient pilot data to establish feasibility, safety power calculations and define an optimal study protocol.

1.6 Study design

This study aims to observe the association between perioperative intravenous fluids have and renal function in adult patients undergoing major surgery. **It is a single-centered, prospective observational study and therefore does not change the standard of care in any way.** All patients undergoing surgery at Austin Hospital will be given the perioperative fluids at discretion of the treating clinicians.

The study will be conducted over a 12-week period, allowing a wide variety of amount and type of fluids given to the patients. Austin Hospital staff specialists in anaesthesia agree that on the basis of current evidence, Saline (0.9%), Plasmalyte or Hartmann's solution are equally acceptable for crystalloid fluid therapy in every situation requiring major surgery with the exclusion of surgery for liver transplantation where specific hospital perioperative fluid protocols are used in these settings.

As there is no departure from standard care for this study, Saline (0.9%), Plasmalyte and Hartmann's solution will be available for administration to all patients undergoing major surgery. In the situations, where, in the opinion of the treating anaesthetist or clinician, there is a clinical indication for other types of fluid e.g. colloids, blood, dextrose etc, again there will be no deviation from standard care in any way.

All adult patients who undergo major surgery will be analysed. The primary outcome will be the proportion of patients with kidney injury or failure based on established criteria[5]. Secondary outcomes will include delta creatinine (the difference between baseline and peak creatinine), serum electrolyte levels, acid base disturbances, requirements for ICU, duration of ICU stay, hospital length of stay, complications and in-hospital mortality.

All of the data required for this study are collected routinely as part of standard clinical care and/or quality assurance activities[6].

1.7 Study importance

This study will establish the preliminary efficacy evidence base for the design of a larger blinded interventional study (The SPLIT Study, HREC/12/Austin/161), which has been submitted to the Austin Research Ethics Unit and is currently being considered for approval.

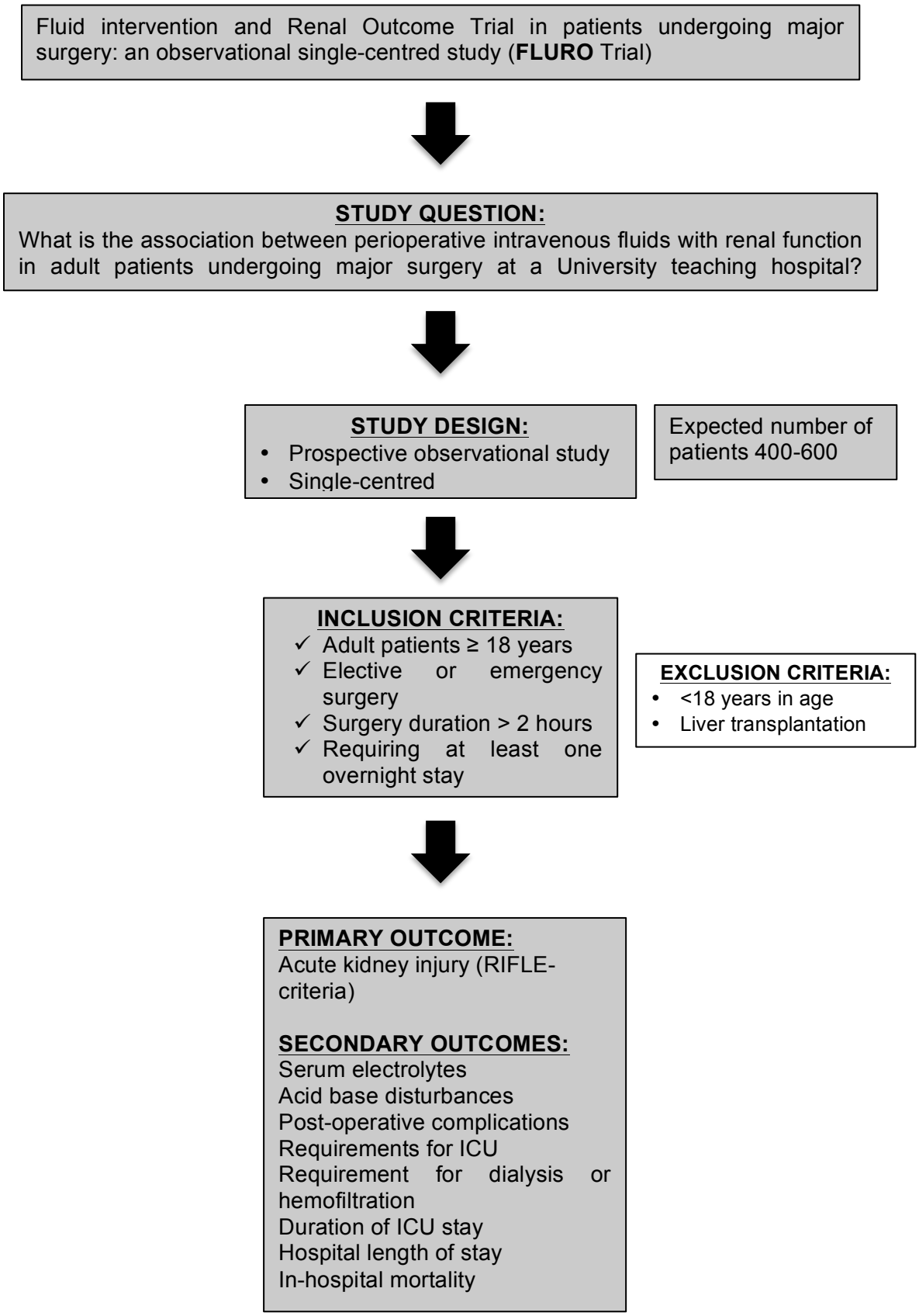
1.8 Hospitals involved

Austin Hospital

1.9 Number of participants

Given the current theatre workload at Austin Hospital, 400-600 participants will be recruited.

FLOW DIAGRAM



RESEARCH QUESTION

What is the association between perioperative intravenous crystalloids with renal function in adult patients undergoing major surgery at a University teaching hospital?

BACKGROUND AND RATIONALE

For all patients undergoing major surgery, two important and fundamental goals in fluid intervention include the maintenance of intravascular volume to ensure optimal organ perfusion and function, and the avoidance of metabolic and electrolyte disturbances that can compromise organ function.

Worldwide, the most commonly used crystalloid fluids available for all patients undergoing surgery include:

1. Hartmann's solution
2. Saline (0.9%)
3. Plasmalyte solution

The electrolyte composition of some of these commonly used crystalloid fluids are summarised in Table 1. All these solutions have similar sodium concentrations (130-150 mmol/L) and may contain physiological concentrations of potassium (Hartmann's and Plasmalyte solutions). There are however some major differences in anion composition. All three solutions above have chloride as a major anionic constituent, the balance in Hartmann's and Plasmalyte solutions being made up of lactate and acetate respectively. Both lactate and acetate are ultimately metabolised by the liver to bicarbonate, thus producing a near ideal physiological solution. Because their electrolyte composition is similar to plasma, they are frequently called "balanced" crystalloid solutions.

Pre-clinical and early clinical data suggest that saline may give rise to adverse effects including immune dysfunction[7], gastrointestinal dysfunction[8] and decreased renal cortical perfusion and renal blood flow[9]. There is strong expert opinion that 'normal saline' or Saline (0.9%) is neither "normal" nor "physiological"[10]. In fact, it has approximately 1.5 times more chloride than normal plasma and its use can lead to hyperchloraemic acidosis[3]. Although hyperchloraemic acidosis may be a benign phenomenon[11,12], recent data raise the possibility that the use of saline for fluid resuscitation in adult ICU patients may lead to an increased risk of developing acute kidney injury compared to resuscitation fluids with a lower concentration of chloride such as Plasmalyte[2,13].

In a single-centred prospective open-label sequential period pilot study of 1533 critically ill patients, the implementation of a chloride-restrictive strategy that included avoiding the use of normal saline was associated with a significant decrease in the incidence of acute kidney injury and use of renal replacement therapy[2]. Similarly, a large retrospective study of adults undergoing major open abdominal surgery suggested that, compared to saline, the use of Plasmalyte was associated with a

decreased risk of major complications including the development of renal failure requiring dialysis[13].

Plasmalyte is a crystalloid that more closely resembles plasma with a more physiological chloride concentration and pH (Table 1). Yet, there is a lack of well-designed prospective studies comparing Plasmalyte to other crystalloid solutions. The direct measurement of the "unmeasured" anions acetate and gluconate has recently been investigated by Davies et al[14]. Thirty adult patients were systematically randomized to 1:1 to CPB prime with either bicarbonate-balanced fluid (24 mmol/L bicarbonate) or Plasmalyte. Acetate concentrations (normal 0.04 - 0.07 mmol/L) became markedly elevated at 3 minutes after CPB commencement, where the Plasmalyte group (median 3.69, range [2.46 - 8.55]) exceeded the bicarbonate group (0.16 [0.02 - 3.49], P <0.0005). Immediately before CPB separation, levels had declined but the differential pattern remained apparent. Normal circulating acetate concentrations were not restored until 4 hours post separation from CPB.

Similarly gluconate concentration profiles and inter-group differences were seen, with a slower decay immediately before CPB separation. IL-6 increased across CPB, peaking at 4 hours post separation from CPB, with no clear difference between groups. To date this is the only study to demonstrate that acetate containing prime solutions result in supra-physiological plasma concentrations of acetate. The use of acetate-free prime fluid in CPB significantly reduced but did not eliminate large acetate surges in cardiac surgical patients.

Acetate surges in the vasculature may not be benign. In renal replacement therapy, the pro-inflammatory, vasodilatory, myocardial depressant and hypoxaemia promoting properties of acetate[8-14] has led to its removal from contemporary renal replacement fluids. Acetate remains an integral component of commonly used CPB pump prime solutions. Prior to the Davies paper[14], little was known of the acetate concentration profile and consequent physiological impact during cardiac surgery incorporating exposure to acetate-based fluid. The situation concerning gluconate is equally unclear, despite its widespread use.

It therefore remains unresolved from whether the demonstrated supra-physiological concentrations of acetate or gluconate can cause harm. The answer cannot be found in small non-randomised, incompletely matched cohort study, particularly since substitution of bicarbonate in the circuit prime in the Davies study[14] failed to eliminate exposure to supra-physiological concentrations of acetate and gluconate. However, there is already unequivocal evidence of acetate toxicity in contexts other than CPB. A number of studies have documented hypoxia and hypotension when patients with end stage renal disease were dialysed against solutions containing acetate[16-18]. There is also evidence of cytokine release, carbohydrate intolerance, disturbances of fatty acid synthesis, reduction of cytosolic redox potential, intracellular accumulation of phosphate, pyrophosphate, phosphorylated intermediates and calcium, and deposition of intra-mitochondrial calcium and magnesium pyrophosphate[17].

Acetate has also been implicated in direct myocardial toxicity. Patients with chronic renal failure receiving acetate-free haemodiafiltration achieved better stroke volumes, demonstrated a lesser reduction in peripheral resistance and recorded smaller troponin increases than patients receiving conventional acetate-based dialysis[20]. In an isolated perfused rat heart model, exposure of myocardial tissue to acetate concentrations as low as 5 mmol/L resulted in impaired fatty acid oxidation and decreased ATP turnover[19]. Finally, Plasmalyte 148, although promoted as a resuscitation solution, performed poorly in a haemorrhagic shock model. Traverso et

al compared four resuscitation crystalloids[21], and found that Plasmalyte was associated with a lower survival and a late rise in plasma L-lactate concentrations as compared with normal saline and Ringer's lactate solutions.

Acetate-based haemodialysis in Australia and elsewhere has been abandoned, even in supplementary concentrations although it continues to be an integral component of 'balanced' resuscitation fluids, CPB priming solutions and total parenteral nutrition. During CPB, adverse effects triggered by acetate exposure would be difficult to detect amongst the vigorous metabolic and host defence responses to surgery[22], hypothermia, and non-pulsatile blood flow. Although there is no proven detrimental effect, the concentrations reported by Davies suggest a need for further investigations into the safety of acetate containing fluids. At present acetate still remains an integral component of commonly used cardiopulmonary pump prime solutions, and to date there is no clinical evidence to suggest that supra-physiological concentrations of the acetate anion could cause harm. Recently, plasmalyte has been extensively used in patients undergoing major abdominal surgery and recent evidence suggests that it may exert renoprotective compared to normal saline[13].

Hartmann's solution has been widely recommended in the medical literature as it causes less acidosis than saline[23-27]. However, Hartmann's solution is not completely balanced when compared with plasma: with a higher chloride and lower pH. Some authors have questioned whether the lactate in Hartmann's solution may aggravate the lactic acidosis and/or alter the sensitivity and specificity of plasma lactate as a prognostic marker, including after liver resection[28]. In the context of liver resection surgery, liver dysfunction, which can be pre-existing and/or as a result of a reduction in liver capacity after liver resection, can impair the metabolism of lactate found in Hartmann's solution. This may result in iatrogenic hyperlactaemia, which may confound the clinical picture if plasma lactate is being used as a marker of critical illness. Plasma lactate has been demonstrated to be an important prognostic marker after liver resection, correlating well with an increased risk of complications and death[28,29]. Because of these reasons some authors have suggested avoiding Hartmann's solution during liver resection despite a lack of evidence[30].

While current data are of insufficient quality to recommend practice change[4], establishing the relative efficacy and safety of using Saline (0.9%) compared to Plasmalyte or Hartmann's solution in acutely ill adults is now an important research priority. It is equally important to understand the association of these fluids with renal injury in the perioperative setting.

No large-scale interventional trial has compared Saline (0.9%) to a lower chloride crystalloid solution. Both Plasmalyte and Hartmann's solution are the logical comparators to Saline (0.9%) for a large-scale crystalloid trial. There may be additional clinical advantages of Plasmalyte over Hartmann's solution because, unlike other commercially available low-chloride crystalloid solutions, Plasmalyte is compatible with blood products preserved in citrate-based anticoagulation solutions because it does not contain calcium[3] and also because it contains a more physiological concentration of chloride than any other crystalloid solution. In addition Plasmalyte does not contain the anion lactate, which is an important marker of illness severity as outlined above.

Large-scale fluid trials using conventional randomised controlled trials are feasible; however, they are extremely expensive and time-consuming to conduct and can only be justified if initial work in the population of interest (major surgery patients) provides preliminary evidence of a possible effect.

The recently completed CHEST study comparing Saline (0.9%) to the colloid hydroxyethyl starch for fluid resuscitation in intensive care trial[31] in which the Austin Hospital was involved randomised 7000 patients and took 10 years to from inception to publication and cost approximately $5 million dollars to complete.

This proposal outlines a research approach that has the potential to provide key preliminary information and data for logistic feasibility, amounts of fluids used, safety data on the incidence of adverse events and preliminary outcome data for power calculations. Such information is crucial to the design of future trials.

Table 1. Concentration of ions the available crystalloid fluids at Austin Hospital*

Strong Ion	Plasma**	Plasmalyte	Saline(0.9%)	Hartmann's
Sodium (Na^+), meq/L	140 (135 to 145)	140	150	150
Chloride (Cl^-), meq/L	102 (98 to 108)	98	150	150
Potassium (K^+), meq/L	4.0 (3.5 to 5.0)	5	0	0
Calcium (Ca^{2+}), meq/L	2.4 (2.3 to 2.6)	0	0	0
Magnesium (Mg^{2+}), meq/L	2.0 (1.4 to 2.4)	3.0	0	0
Acetate, meq/L	0	27	0	0
Gluconate meq/L	0	23	0	0
Lactate, meq/L	1.0 (0.5 to 2.0)	0	0	0
Strong Ion Difference meq/L	44	49	0	0

*All fluids are manufactured by Baxter Healthcare, Toongabie, NSW.
**Median, Reference Range

FEASIBILITY AT AUSTIN HOSPITAL

The departments of Anaesthesia and Intensive Care at Austin Hospital have completed 6 fluid intervention studies, and currently there is one fluid intervention study still underway in the setting of renal transplantation.

Fluid intervention in liver resection

Recently, the authors completed a multicentre randomized double-blind controlled multicentre study of Plasmalyte vs. Hartmann's solution in patients receiving liver resection[32]. Participants were randomized to Plasmalyte or Hartmann's solution for intraoperative fluid intervention. Primary outcome: base-excess immediately after surgery. Secondary outcomes: lactate levels, strong-ion-difference (SID), total weak acids, net-unmeasured-ions, changes in liver enzymes, perioperative complications and duration of hospital stay.
Results: 60 participants were recruited from 4 tertiary-level hospitals. Both groups were matched according to baseline characteristics, extent of resection, and surgery duration. There were no differences in the volume of trial fluid used, perioperative fluid balance, or urine output. Plasmalyte was not inferior to Hartmann's for the

primary endpoint. Plasmalyte base-excess was 0.8mmol/L greater (95%CI: -0.4 to 2.0;P=0.18). This was associated with hyperchloraemia (Difference 1.7mmol/L, 95%CI: 0.2 to 3.2mmol/L, p=0.03) and hyperlactaemia (Difference 0.8mmol/L, 95%CI: 0.2 to 1.3mmol/L; P=0.01) in the Hartmann's group. In the Hartmann's group 23 patients (77%) had a lactate above the reference range compared to 14 patients (47%) in the Plasmalyte group, P=0.02. Complications were more frequent in the Hartmann's Group (56% vs. 20%, 95%CI: 1.3 to 6.1;P=0.007). Median length of hospital stay: 5.9 days vs. 7.8 days (P=0.041) favouring Plasmalyte group.
Conclusion: For patients undergoing liver resection use of Plasmalyte solution resulted in improved acid base haemostasis, less hyperlactaemia, reduced perioperative complications and a shorter length of hospital stay compared to patients receiving Hartmann's solution.

Fluids and cognitive function in healthy volunteers

In another study, the authors tested the hypothesis that saline infusion would produce greater cognitive changes than Plasmalyte in healthy volunteers[33].
With Ethics Committee approval, we conducted a randomized, crossover, blinded study of healthy adult volunteers. On separate days participants were randomized to 30 ml/kg over one hour of either saline or Plasmalyte. Plasma chemistry was tested on venous samples. As part of a battery of cognitive tests our primary end point was the reaction time index. We studied 25 participants. Plasma chloride was greater after saline, difference 5.4 mmol/L (95%CI: 4.1 to 6.6 mmol/L, P<0,001) associated with greater metabolic acidosis: base-excess 2.5 mmol/L more negative (95%CI: 1.9 to 3.0 mmol/L more negative, P <0.001). There were no important differences in reaction time index between the two arms of the study. After saline, the mean reaction time index was 411 (SD: 63) msec, and after Plasmalyte was 385 (SD: 55) msec: saline 9 msec slower (95 CI: 12 msec faster to 30 msec slower, P = 0.39). None of the other cognitive and mood tests differed.
We concluded that despite significant differences in plasma chemistry, reaction times after saline did not differ from reaction times after Plasmalyte. Further, other measures of cognition did not differ. This finding was contrary to our hypothesis. We cannot exclude differences with Hartmann's solution, however, cognitive differences associated with mild hyperchloremic metabolic acidosis seem unlikely.

Fluid intervention in cardiac surgery

The authors have successfully completed 4 fluid intervention studies in the setting of cardiac surgery.

Most recently, we examined the effect of pump prime on acidosis, strong-ion-difference and unmeasured ions during cardiopulmonary bypass in a randomized blinded clinical trial[34]. There are no studies comparing the mechanism of metabolic acidosis during cardiopulmonary bypass (CPB) using Hartmann's solution and Plasmalyte as pump primes, therefore we tested the hypothesis that the effects of these crystalloids on acidosis is a function of their individual strong ion differences (SID) and unmeasured anions. After Ethics approval we performed a randomised blinded study of 38 adult patients undergoing elective CABG or valve replacement requiring CPB. Both groups received a prime solution of 2000mL; one group with anions lactate and chloride (Hartmann's), the other with anions acetate, gluconate and chloride (Plasmalyte). Endpoints were standard base deficit, SID, total weak acids, and strong ion gap (SIG). Serum electrolytes and arterial blood gases were collected at 6 intervals: immediately prior to CPB (T0), then 2min (T1), 5min (T2), 10min (T3), 30min (T4), and 60min (T5) post CPB. On delivery of pump prime both groups developed at metabolic acidosis – Plasmalyte® (base excess: 0.53mmol/L

(T0) to -3.03mmol/L (T1), P=0.001, Hartmann's; base excess: 0.42mmol/L (T0) to -2.20mmol/L (T1), P=0.001. Lactate remained unchanged in the Plasmalyte group, however peaked with Hartmann's at 2min: 0.15mmol/L (T0) to 4.5mmol/L (T1), P=0.001, returning to baseline by 60minutes. There was significant hyperchloraemia with Hartmann's compared to Plasmalyte. The SID with Plasmalyte® increased from 37.6mEqu/L (T0) to 40.3mEqu/L (T1), P=0.001, remaining elevated at 60minutes (36.7mEqu/L). Conversely with Hartmann's, the SID decreased from 36.3mEqu/L (T0) to 31.2mEqu/L (T1) and remained decreased at T5 (33.3mEqu/L). The SIG increased significantly from T0 to T1 with Plasmalyte® (1.1mEqu/L to 11.9mEqu/L, P=0.001), but marginally with Hartmann's (-0.6mEqu/L to 2.0mEqu/L). We concluded that the mechanism of acidosis during CPB with Hartmann's solution was due to combination of iatrogenic hyperlactaemia and hyperchloraemia. In contrast the mechanism with Plasmalyte was a production of unmeasured anions, most likely acetate and gluconate.

Second, we previously studied acid-base changes during CPB with polygeline pump prime and defined and quantified the factors, which contribute to metabolic acidosis[25]. Using quantitative biophysical methods, we demonstrated that in patients receiving a pump prime rich in chloride and polygeline, the metabolic acidosis of CPB was mostly due to iatrogenic increases in serum chloride concentration and unmeasured strong anions.

Its development was partially attenuated by iatrogenic hypoalbuminaemia. Changes in lactate concentrations did not play a role in the development of metabolic acidosis in our patients.

Because the development of metabolic acidosis during cardiopulmonary bypass was well recognized but poorly understood, in another study we hypothesized that the delivery of pump prime fluids is primarily responsible for its development[26]. We studied acid-base changes induced by the establishment of CPB using two types of priming fluid (Haemaccel, a polygeline solution, and Ringer's Injection vs. Plasmalyteusing quantitative biophysical approach). Immediately on delivery of pump prime fluids, all patients developed a metabolic acidosis. The decrease in base excess was the same for both primes (4.60 vs. 4.37; not significant). However, the mechanism of metabolic acidosis was different. With the Haemaccel-Ringer's prime, the metabolic acidosis was hyperchloremic, whilst with Plasmalyte, the acidosis was induced by an increase in unmeasured anions, most probably acetate and gluconate, although these were not directly measured. The resolution of these two processes was different because the excretion of chloride was slower than that of the unmeasured anions. This study demonstrated that cardiopulmonary bypass–induced metabolic acidosis was iatrogenic in nature and derived from the effect of pump prime fluid on acid-base balance.

Finally, we tested the hypothesis that a cardiopulmonary bypass prime with lactate would be associated with less acidosis than a prime with only chloride anions because of differences in the measured strong-ion-difference. We randomised 20 patients to a 1500 ml bypass prime with either a chloride-only solution (Ringer's Injection) or a lactated solution (Hartmann's solution). We found that the chloride-only group had greater acidosis with lower base-excess and pH. Contrary to our hypothesis, however, the difference between the groups was not due to a difference in the measured strong-ion-difference. When the difference in standard base-excess between the groups was greatest, the difference in the measured strong-ion-difference was only very small. There was however, a difference in the net-

unmeasured-ions (strong-ion-gap). We concluded that acid-base changes with cardiopulmonary bypass might differ with the prime but that the early differences between chloride-only and lactated primes appear not to be due to differences in the measured strong-ion-difference. We suggested that future studies examine other possible mechanisms including unmeasured ions.

Fluid intervention in renal transplantation

Currently the authors are half way through a randomised trial evaluating the use of either Saline (0.9%) or Hartmann's solution in patients undergoing renal transplantation[35]. We hypothesised that the balanced crystalloid fluid Plasmalyte, will have more favourable effects on metabolic acidosis and early graft function compared to Saline (0.9%). Adult patients (age > 18 years) undergoing deceased donor renal transplantation (heart-beating or non heart-beating) are included with the primary endpoint being base deficit immediately post surgery in the Post Anaesthesia Care Unit and at 24 & 48 hours postoperatively. A variety of secondary outcomes are being measured including potassium levels, strong-ion-difference, renal biomarkers, requirements for postoperative dialysis, adverse events and hospital stays (days). We have completed recruitment of 20 patients with a total of 50 participants expected. There are no results at this early stage.

The department of anaesthesia and intensive care have an established research infrastructure and have participated in a number of large-scale studies leading to a number of recent NEJM publications[36-40].

CHEST Study and SAFE Studies

Of note, the Austin Hospital contributed substantially to the 7000-patient RCT comparing Saline (0.9%) to the colloid hydroxyethyl starch for fluid resuscitation in intensive care, which was recently published in the NEJM[31]. In addition, the ICU at Austin Hospital was a major recruiting centre for the multicentre, randomized, double-blind SAFE trial that compared the effect of fluid resuscitation with albumin or Saline (0.9%) on mortality in a heterogeneous population of patients in the ICU[41]. This has been one of the most widely sited fluid intervention studies in the world.

1.10 Summary

This is an observational study; there is no departure from standard care at any stage. It involves the collection of data that has already been collected for clinical or quality assurance purposes.

In this study we will be collecting information about intravenous fluid intervention (type of fluid and amount) for adult patients undergoing major surgery (duration >2 hours and at least one overnight stay). Data will be collected over a 12-week period. Specifically, the association of these fluids with kidney function will be investigated. Perioperative care and fluid intervention therefore will remain completely at the discretion of the treating clinicians.

The current study will inform clinicians looking after patients undergoing major surgery about the effects of these fluids on renal injury.

This study will be also be used in Fulfilment of University of Melbourne BSc Honours Project for Ms Angelica Armellini.

OBJECTIVES

The overall objective of this study is to determine the association between perioperative intravenous fluids and renal function in adult patients undergoing major surgery.

The choice of perioperative intravenous fluid intervention such as Saline (0.9%) vs. Plasmalyte vs. Hartmann's solution will be entirely at the discretion of the all clinicians caring for the patients.

Specifically, we aim to establish the association of Saline (0.9%), Plasmalyte and Hartmann's solution on:

1. The development of acute kidney injury in hospital
2. The development of biochemical and acid-base derangements
3. The development of postoperative complications
4. Requirements for ICU
5. Requirement for dialysis or hemofiltration
6. Duration of ICU stay
7. Hospital length of stay
8. Hospital mortality

STUDY DESIGN

1.11 General

This study is a single-centred prospective observational study on the effects of intravenous fluids on renal function in adult patients undergoing major surgery.

1.13 Inclusion criteria

Patients aged ≥18 years admitted to the Austin Hospital who receive major surgery. For the purpose of the study, major surgery will be defined as any surgery longer than 2 hours and requiring a least one night of post-operative hospital stay.

1.14 Exclusion criteria

- Patients who are <18 years in age
- Patients undergoing liver transplantation (these patients require specific crystalloid solutions as part of the Austin Hospital perioperative fluid intervention protocol).

1.15 Baseline data

The following baseline data will be collected:

- Age

- Gender
- Admission type (elective vs. emergency)
- Type of surgery (hepatobiliary, colorectal, upper GI, orthopaedic etc.)
- If admitted to ICU: Chronic APACHE co-morbidities (including long-term dialysis)
- If admitted to ICU: APACHE-III admission diagnosis[42]
- If admitted to ICU: Illness severity based on the on the APACHE-III risk of death score[42]
- Baseline creatinine.
- Baseline biochemistry

(Note: - all of these data are routinely collected for quality assurance purposes or as measured as part of usual clinical care)

1.16 Study treatments

This is not an interventional study. This is an observational study only. Therefore, there is no departure from standard care at any stage. It only involves the collection of data that has already been collected for clinical or quality assurance purposes. Perioperative care and fluid intervention will remain completely at the discretion of the treating clinicians.

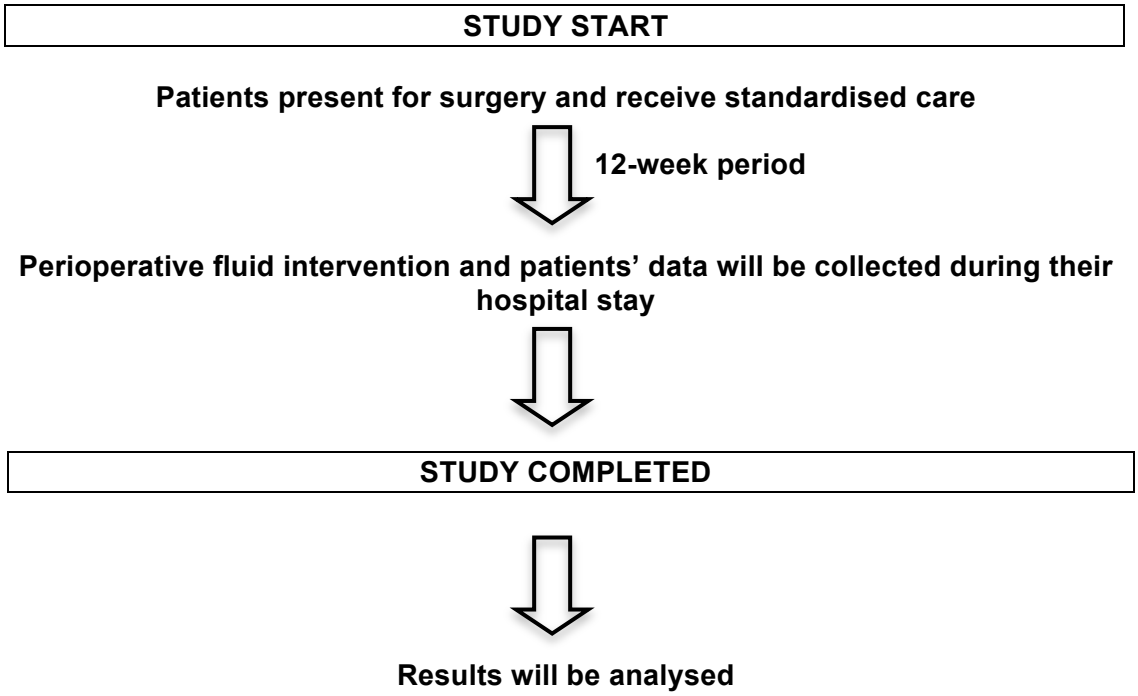
1.17 Treatment allocation

Non-applicable. There is no departure from standard care at any stage. It only involves the collection of data that has already been collected for clinical or quality assurance purposes.

Total study duration: 12 weeks

TREATMENT SCHEME

All adult patients (≥18 years) undergoing major surgery (> 2 hours) and requiring at least one overnight post-operative hospital stay:



Outcome measures

1.17.1 General

The primary outcome measure will be acute kidney injury (RIFLE-criteria) defines as AKI, defined as an increase in creatinine greater than 25% or 0.5 mg/dL (44 µmol/L) from baseline to peak value within the first 48-hours postoperatively.

1.17.2 Secondary outcome measures

- Serum electrolytes
- Acid base disturbances
- Post-operative complications
- Requirements for ICU
- Requirement for dialysis or hemofiltration
- Duration of ICU stay
- Hospital length of stay

ETHICS

1.18 Guiding principles

This study is to be performed in accordance with World Medical Association Declaration of Helsinki: Ethical principles for medical research involving human subjects (WMA 2008), the International Ethical Guidelines for Biomedical Research Involving Human Subjects (CIOMS 2002) and the National Statement on Good Practice in Human Research.

The research utilises information normally gathered during the course of the delivery of a currently recognised treatment and will maintain anonymity and privacy and can therefore be conducted in accordance with Australian Law and the National Statement.

1.19 Ethical and legal issues in this study

Patterns of practice in different hospitals are often idiosyncratic and unscientific[22]. Indeed, much of clinical medicine remains empirical and local medical opinion and supply of resources are often more important than science in determining how medical care is delivered[22]. Wide variations that characterise usual clinical practice often have no basis in science but may have important implications for patient outcomes. Where there are two distinct approaches being employed in different institutions, we believe that there is an ethical imperative to conduct research to establish which approach is best.

This study utilises a novel design in order to assess the relative effects of perioperative intravenous fluids therapy. This study is clearly an observational study on the basis of conventional guidelines. **Specifically, the study involves no departure from standard care and does not involve the collection of any data that are not already being collected for clinical and/or quality assurance purposes.**

In this study, whether or not the patients receive saline, Hartmann's solution or Plasmalyte as default crystalloid fluid therapies, will be determined by the treating clinicians. No controls will be placed on the use of colloidal fluid therapy, blood products (red blood cells, platelets, cryoprecipitate or fresh frozen plasma) or any other fluid non-crystalloid fluid intervention (e.g. dextrose, bicarbonate).

All patients in this study will receive standard perioperative care.

This study involves negligible risk.

1.20 Confidentiality of patient data

Patients will be allocated a unique study number. Study data will be obtained from routinely collected quality assurance and clinical information. Data entered into the study database will be identified by the unique study number only. The enrolment log and the study data will be kept separately.

DATA MANAGEMENT

1.21 Data collection methods

The demographic, biochemical, and outcome data used in this study are already collected by the Austin Hospital for administrative and quality assurance purposes[7].

Any ICU data are similarly collected and already provided to the Australian and New Zealand Intensive Care Society Centre for Outcome and Resource Evaluation as part of a government-funded bi-national quality assurance programme.

The only data used in this study, which are not routinely collected for quality assurance purposes, are the daily volume of study fluid administered as fluid boluses and the data relating to renal outcomes. These data will be collected by the Principle and Associate invesigators.

1.22 Data management

De-identified data management will be performed by the Australian and New Zealand Intensive Care Research Centre (ANZIC-RC) located within the School of Epidemiology and Public Health of Monash University.

1.23 Protocol deviation

A protocol deviation is generally an unplanned excursion from the protocol that is not implemented or intended as a systematic change. The principle investigators will be responsible for ensuring the study is conducted in accordance with the procedures and evaluations described in this protocol and will protect the rights, safety, and welfare of all subjects. The principle investigator will not implement any deviation from, or changes of, the protocol, unless it is necessary to eliminate an immediate hazard to trial subjects.

For the purposes of this protocol, any deviations requiring notification to the Research Ethics Committee will be defined as any participant who

- Entered into the study even though they did not satisfy the entry criteria.
- Developed exclusion criteria during the study and not withdrawn.

When a deviation from the protocol is identified for an individual subject, the chief investigator will assess the deviation and the possible impact to the safety and/or efficacy of the subject to determine the continuation in the study. If a deviation impacts the safety of a subject, the principle investigator will inform the Research Ethics Committee in accordance with normal Hospital processes.

SAFETY CONSIDERATIONS

1.24 Adverse Events and Other Safety Aspects

Safety will be assessed throughout the study. As part of normal hospital care for all patients undergoing surgery at Austin Hospital, a complete baseline profile of each subject will be established by the treating surgical unit through medical history, clinical laboratory values, vital signs, physical assessments, and ECGs. During the course of the study, surgical and anaesthesia care, including vital signs, complete and targeted physical assessments, laboratory tests, and ECGs will be performed at in accordance with normal hospital protocols. **There will be no deviation from standard care at any time point.**

All medical and surgical changes from baseline will be monitored throughout the study by the treating units and appropriate interventions will be taken accordingly.

STATISTICAL CONSIDERATIONS

1.25 Power calculations and sample size

A recently published open label sequential period study of chloride-liberal vs. chloride-restrictive fluid administration[2] demonstrated a reduction in the incidence of injury and failure based on RIFLE criteria from 14% (95% CI, 11% - 16%) to 8.4% (95% CI, 6.4% - 10%); P<0.001) with the introduction of a chloride-restrictive fluid regime.

Assuming that, as we have conservatively estimated, we can study 400-600 subjects over a 6-week period, our sample size will provide more than 90% power with an alpha of 0.01 to detect a difference of this magnitude between patients treated with saline vs. patients treated with different crystalloid fluids.

1.26 Analysis plan

A complete description of the statistical analyses will be specified in a statistical analyses plan, finalised prior to completion of the study.

All analyses will be conducted on an intention-to-treat basis.

The primary analyses will be unadjusted analyses in which binary outcomes will be compared using relative risks with 95% confidence intervals and chi square tests and continuous outcomes will be compared with the use of mean differences and un-paired T-tests assuming that normality assumptions are meet. If normality assumptions are not met then we plan to attempt simple data transformation, such as a logarithm transformation, and if this fails to proceed to a Mann-Whitney rank based test. Adjusted analyses will be performed using Poisson regression for binary

outcomes and linear regression for continuous outcomes. Baseline covariates will include age, gender, elective vs. emergency surgery, surgical specialty of admission, type of operation, and baseline serum creatinine level. Survival times will be compared using log-rank tests and presented as Kaplan-Meier curves. Multivariable models will be developed to study the predictors of AKI and the independent association between fluid choice and renal outcomes.

1.27 Sub-groups

There will be the following subgroups:

- Patients undergoing abdominal surgery
- Patients undergoing vascular surgery
- Patients undergoing thoracic surgery
- Patients undergoing other surgeries (orthopaedics, urology etc.)
- Patients undergoing emergency surgery

1.28 Randomization process

Not-applicable

1.29 Blinding

Not-applicable

STUDY BUDGET

1.30 Detailed budget

Item	**Year 1**
Computer consumables (printing, paper, ink) **Statistical consultation (free provided by the University of Melbourne as part of honours)** **Application to TGA: non-applicable**	$1000

Total (AUD)	**$ 1000**

1.31 Dispensing and storage costs

Non-applicable. There will be no additional costs incurred for the dispensing of the fluids by Austin Hospital pharmacy beyond that which is already art of normal dispensing practices.

STUDY ADMINISTRATION STRUCTURE

1.32 Department of Anaesthesia & Intensive Care responsibilities

- Overall management of the study will be by both the Department of Anaesthesia and Intensive Care at Austin Hospital
- Both departments will be involved in the case report form design and production
- Both departments will provide assistance for training for Research Co-ordinators and study team if necessary
- Study database set-up and co-ordination of data entry will be conducted by all principle investigators

1.33 Data management responsibilities

- Data queries
- Data analysis

PUBLICATIONS

The study will be published in the name of the of the study investigators. The principle and associate investigators will be listed as authors.

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