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Normal saline versus lower-chloride solutions for kidney transplantation (Review)

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TABLE OF CONTENTS

[Intervention Review]

Normal saline versus lower-chloride solutions for kidney transplantation

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ABSTRACT

Background

The ideal intravenous fluid for kidney transplantation has not been defined, despite the common use of normal saline during the peri-operative period. The high chloride content of normal saline is associated with an increased risk of hyperchloraemic metabolic acidosis, which may in turn increase the risk of hyperkalaemia and delayed graft function. Balanced electrolyte solutions have a lower chloride content which may decrease this risk and avoid the need for dialysis due to hyperkalaemia in the immediate post-transplant period. Randomised controlled trials (RCTs) addressing this issue have used biochemical outcomes to compare fluids and have been underpowered to address patient-centred outcomes such as delayed graft function.

Objectives

To examine the effect of lower-chloride solutions versus normal saline on delayed graft function, hyperkalaemia and acid-base status in kidney transplant recipients.

Search methods

We searched the Cochrane Kidney and Transplant's Specialised Register to 26 November 2015 through contact with the Information Specialist using search terms relevant to this review.

Selection criteria

RCTs of kidney transplant recipients that compared peri-operative intravenous lower-chloride solutions to normal saline were included.

Data collection and analysis

Two independent investigators assessed studies for eligibility and risk of bias. Data from individual studies were extracted using standardised forms and pooled according to a published protocol. Summary estimates of effect were obtained using a random-effects model, and results were expressed as risk ratios (RR) and their 95% confidence intervals (CI) for dichotomous outcomes, and mean difference (MD) and 95% CI for continuous outcomes.

Main results

Six studies (477 participants) were included in the review. All participants were adult kidney transplant recipients and 70% of participants underwent live-donor kidney transplantation. The overall risk of bias was low for selection bias and unclear for remaining domains. There was no difference in the risk of delayed graft function (3 studies, 298 participants: RR 1.03, 95% CI 0.62 to 1.70) or hyperkalaemia (2 studies, 199 participants: RR 0.48, 95% CI 0.04 to 6.10) for participants who received balanced electrolyte solutions compared to normal saline. Intraoperative balanced electrolyte solutions compared to normal saline were associated with higher blood pH (3 studies, 193 participants:

MD 0.07, 95% CI 0.05 to 0.09), higher serum bicarbonate (3 studies, 215 participants: MD 3.02 mEq/L, 95% CI 2.00 to 4.05) and lower serum chloride (3 studies, 215 participants: MD -9.93 mmol/L, 95% CI -19.96 to 0.11). There were four cases of graft loss in the normal saline group and one in the balanced electrolyte solution group, and four cases of acute rejection in the normal saline group compared to two cases in the balanced electrolyte solution group.

Authors' conclusions

Balanced electrolyte solutions are associated with less hyperchloraemic metabolic acidosis compared to normal saline, however it remains uncertain whether lower-chloride solutions lead to improved graft outcomes compared to normal saline.

PLAIN LANGUAGE SUMMARY

Normal saline versus lower-chloride solutions for kidney transplantation

What is the issue?

People with kidney failure may have a kidney transplant to replace the function of their own kidneys. During a kidney transplant operation, patients receive fluids through their veins to keep them hydrated. Maintaining good hydration helps the transplanted kidney to work after the operation. The choice of fluids that are given during and after the operation may have an effect on how the transplant kidney works after surgery and on the patient's acid-base measures in the blood.

Normal saline is a type of fluid that is commonly given during an operation. It contains a high chloride level. Giving a kidney transplant patient normal saline might increase the acid level of the blood compared to giving the patient fluids that contain less chloride. High blood acid levels might be associated with high blood potassium levels, which is dangerous for the heart and often requires dialysis to correct.

What did we do?

We performed a systematic review to address the question of whether giving lower-chloride fluids compared to normal saline during the kidney transplant operation alters the early function of the kidney, the number of patients with high blood potassium levels, and the acid level in the blood after the operation. We included studies that were published up to November 26, 2015.

What did we find?

We found six studies that included 477 kidney transplant patients. The majority of these patients had a kidney transplant from a living donor. The overall quality of the studies was low to average, and the main problem was the small number of studies and the small size of the studies. There was no information on funding source for most of the studies.

Compared to normal saline, giving kidney transplant patients solutions that contain less chloride during their transplant operation resulted in lower blood acid levels but did not affect how the transplant kidney worked after surgery, or the number of patients who had high blood potassium levels. Harmful effects were not reported in many studies. In the group of patients who were given lower-chloride fluids, the transplant failed in one patient and one patient rejected the transplant. In the group of patients who were given normal saline, the transplant failed in four patients, and two patients rejected the transplant. However, this is probably an incomplete picture of harmful effects.

BACKGROUND

Description of the condition

End-stage kidney disease (ESKD) is a major cause of morbidity and mortality worldwide and was estimated to affect 1738 per million population in the USA in 2009, with 72% of these undergoing maintenance haemodialysis (Collins 2012). Australian registry data from 2010 estimated that 850 per million population receive renal replacement therapy, comprising of both dialysis patients and kidney transplant recipients (ANZDATA 2011). Kidney transplantation offers a significant survival benefit compared to dialysis and is the treatment of choice for the majority of patients. However, transplantation is limited by the number of available donor organs, and strategies that improve short- and long-term graft function are important in the effective utilisation of this resource.

Delayed graft function has been variably defined as a failure of the serum creatinine to fall by 20% within the first 72 hours post-transplantation, or a requirement for dialysis within seven days post-transplant (Yarlagadda 2008). Delayed graft function has been associated with poorer short- and long-term outcomes, including prolonged hospitalisation, higher transplantation costs, increased risk of acute rejection and decreased five-year graft survival (Yarlagadda 2009). Delayed graft function is dependent on multiple factors, including donor type, comorbidities, and ischaemic time. In addition, the peri-operative fluid status of the recipient and the regimen of fluid therapy are a possible consideration. While it is well accepted that maintaining adequate peri-operative fluid volume facilitates early graft function (Schnuelle 2006), the type of fluid that is administered varies substantially between transplant units.

Description of the intervention

Normal saline, or 0.9% saline, contains 154 mmol/L of sodium chloride and is a widely accessible and commonly used fluid in kidney transplantation. A survey of United States transplant units demonstrated that normal saline is the most commonly used peri-operative fluid for kidney transplantation (O'Malley 2002). However, there are concerns that the high chloride content of this solution leads to a hyperchloraemic metabolic acidosis (Handy 2008; Roche 2007; Scheingraber 1999). In response to this acidosis, potassium is released into the extracellular space in exchange for hydrogen ions as a compensatory mechanism (Halperin 1998), which may lead to the development of hyperkalaemia (O'Malley 2005). Hyperkalaemia is an indication for dialysis post-transplant and may compromise the cardiovascular stability of the transplant recipient; in particular by increasing the risk of hyperkalaemia associated cardiac arrhythmias (Halperin 1998). Furthermore, the administration of normal saline has been associated with renal vasoconstriction and decreased kidney perfusion (Chowdhury 2012; Wilcox 1983), as well as an increased risk of acute kidney injury in critical care and general surgical populations (Yunos 2012; Shaw 2012). In the setting of kidney transplantation, these findings may support the hypothesis that normal saline could increase the risk of delayed graft function.

Lower-chloride solutions refer to fluids with a lower chloride content compared to normal saline, and include both balanced electrolyte solutions and colloids. Balanced electrolyte solutions refer to crystalloid fluids that contain a more physiological level of chloride as well as bicarbonate precursors, and include fluids such as compound sodium lactate and Plasma-lyte®. These fluids have been advocated in the setting of kidney transplantation as they are thought to limit the development of hyperchloraemic metabolic acidosis and subsequent hyperkalaemia, despite the fact that they contain potassium at a physiological concentration (Table 1). However, others caution the use of these fluids due to the risk of hyperkalaemia resulting from the potassium present in these fluids (Schnuelle 2006).

Why it is important to do this review

There have been a number of small randomised controlled trials (RCT) that have compared normal saline to certain balanced electrolyte solutions. However, the majority have assessed acid-base measures as a primary outcome and were underpowered to address clinical endpoints such as delayed graft function or hyperkalaemia requiring dialysis (Hadimioglu 2008; Khajavi 2008; O'Malley 2005). In addition, none have addressed long-term outcomes of graft or patient survival.

OBJECTIVES

The aims of this review were to compare normal saline to lower-chloride containing solutions, in particular balanced electrolyte solutions and colloids, as fluid therapy in the acute peri-transplant period.

METHODS

Criteria for considering studies for this review

Types of studies

We included RCTs and quasi-RCTs (RCTs in which allocation to treatment was obtained by alternation, use of alternate medical records, date of birth or other predictable methods) that compared normal saline to lower-chloride solutions without language restriction.

Types of participants

We included adults and children who received first or subsequent deceased-donor or living-donor kidney transplants.

Types of interventions

We included studies that compared intravenous normal saline to lower-chloride solutions during the intraoperative and immediate postoperative period following kidney transplantation. There was no restriction on the volume or rate of fluid delivery.

Lower-chloride solutions included:

1. Balanced electrolyte solutions: compound sodium lactate (also known as Hartmann's solution or Ringer's lactate), Plasma-lyte® and Elo-Mel isoton®
2. Other crystalloids: dextrose 5%, dilutions of normal saline
3. Colloids: albumin 4%, gelatins (including Gelofusine® and Haemaccel®) and hydroxyethyl starches in balanced electrolytes (including Hextend®).

We excluded studies that compared fluids types to pharmacological agents (e.g. mannitol, dopamine, frusemide), or blood transfusion. In addition, we excluded colloid fluids that were made up in normal

saline as they have the same chloride content as normal saline (e.g. hydroxyethyl starches in normal saline).

Specific comparisons were made between:

1. Normal saline and balanced electrolyte solutions
2. Normal saline and colloids
3. Normal saline and all lower-chloride solutions.

Types of outcome measures

Primary outcomes

1. Delayed graft function, defined as the need for dialysis within seven days of kidney transplant surgery or failure of the serum creatinine to fall by 20% within 72 hours.
2. Clinically significant hyperkalaemia, defined as serum potassium > 5.5 mmol/L, or any hyperkalaemia requiring treatment (e.g. with dialysis, calcium gluconate, insulin, B_2 agonists, or ion-exchange resins) within the first 72 hours post-transplant.

Secondary outcomes

1. Acid-base status, which was measured as the mean difference in blood pH, serum potassium concentration, serum chloride concentration, and serum bicarbonate concentration at the end of surgery compared to baseline (pre-operative) and at day three compared to baseline (pre-operative).
2. Adverse events, including death, graft loss, or cardiovascular events.

Search methods for identification of studies

Electronic searches

We searched Cochrane Kidney and Transplant's Specialised Register to 26 November 2015 through contact with the Information Specialist using search terms relevant to this review. The Specialised Register contains studies identified from the following sources.

1. Quarterly searches of the Cochrane Central Register of Controlled Trials CENTRAL
2. Weekly searches of MEDLINE OVID SP
3. Handsearching of kidney-related journals and the proceedings of major kidney conferences
4. Searching of the current year of EMBASE OVID SP
5. Weekly current awareness alerts for selected kidney journals
6. Searches of the International Clinical Trials Register (ICTRP) Search Portal and ClinicalTrials.gov.

Studies contained in the Specialised Register were identified through search strategies for CENTRAL, MEDLINE, and EMBASE based on the scope of Cochrane Kidney and Transplant. Details of these strategies, as well as a list of handsearched journals, conference proceedings and current awareness alerts, are available in the Specialised Register section of information about the Cochrane Kidney and Transplant.

See Appendix 1 for search terms used in strategies for this review.

Searching other resources

1. Reference lists of clinical practice guidelines, review articles and relevant studies.
2. Letters seeking information about unpublished or incomplete studies to investigators known to be involved in previous studies.

Data collection and analysis

Selection of studies

We used the search strategy described to obtain titles and abstracts of studies relevant to the review. Two authors independently screened titles and abstracts, and discarded studies that were not applicable; however studies and reviews thought to include relevant data or information were retained initially. Two authors independently assessed retrieved abstracts, and if necessary the full text of these studies, to determine which satisfied the inclusion criteria.

Data extraction and management

Two independent authors extracted the data using standard data extraction forms. Studies reported in non-English language journals were translated before assessment. Where more than one publication of a study existed, reports were grouped together and the publication with the most complete data was used in the analyses. Where relevant outcomes were only published in earlier versions, these data were used. Any disagreement between authors regarding study selection or data extraction was resolved by discussion and referral to a third author where necessary.

Assessment of risk of bias in included studies

The following items were independently assessed by two authors using the risk of bias assessment tool (Higgins 2011) (see Appendix 2).

- Was there adequate sequence generation (selection bias)?
- Was allocation adequately concealed (selection bias)?
- Was knowledge of the allocated interventions adequately prevented during the study?
  - Participants and personnel (performance bias)
  - Outcome assessors (detection bias)
- Were incomplete outcome data adequately addressed (attrition bias)?
- Are reports of the study free of suggestion of selective outcome reporting (reporting bias)?
- Was the study apparently free of other problems that could put it at a risk of bias?

Measures of treatment effect

Dichotomous outcomes (e.g. delayed graft function and hyperkalaemia) were expressed as risk ratio (RR) with 95% confidence intervals (CI). Where continuous scales of measurement were used to assess the effects of treatment (e.g. blood pH, serum potassium, chloride and bicarbonate concentrations), the mean difference (MD) was used, or the standardised mean difference (SMD) if different scales had been used. Adverse effects were assessed with descriptive techniques.

Dealing with missing data

Further information required from the original author was requested by written correspondence and any relevant information obtained in this manner was included in the review. Evaluation of data, including intention-to-treat, losses to follow-up and withdrawals were investigated, and issues of missing data were critically appraised (Higgins 2011).

Assessment of heterogeneity

Heterogeneity was analysed using a Chi^2 test on N-1 degrees of freedom, with an alpha of 0.05 used for statistical significance, as well as with the I^2 test (Higgins 2003). I^2 values of 25%, 50% and 75% correspond to low, medium and high levels of heterogeneity.

Assessment of reporting biases

Funnel plots were used to assess for the potential existence of small study bias (Higgins 2011).

Data synthesis

Data were pooled using the random-effects model but the fixed-effect model was also used to ensure robustness of the model chosen and susceptibility to outliers.

Subgroup analysis and investigation of heterogeneity

Subgroup analysis was used to explore possible sources of heterogeneity (e.g. participants, interventions and study quality). Heterogeneity among participants could be related to age, comorbidities, living versus deceased donor transplants, extended versus standard criteria donor kidneys, number of HLA mismatches, cold-ischaemia time greater or less than 12 hours, and type of immunosuppression. Adverse effects were tabulated and assessed with descriptive techniques. Where possible, the risk difference with 95% CI was calculated for each adverse effect, either compared to no treatment or to another agent.

Sensitivity analysis

We performed sensitivity analyses to explore the influence of the following factors on effect size.

- Repeating the analysis excluding unpublished studies
- Repeating the analysis taking account of risk of bias
- Repeating the analysis excluding any very long or large studies to establish how much they dominate the results
- Repeating the analysis excluding studies using the following filters: diagnostic criteria, language of publication, source of funding (industry versus other), and country.

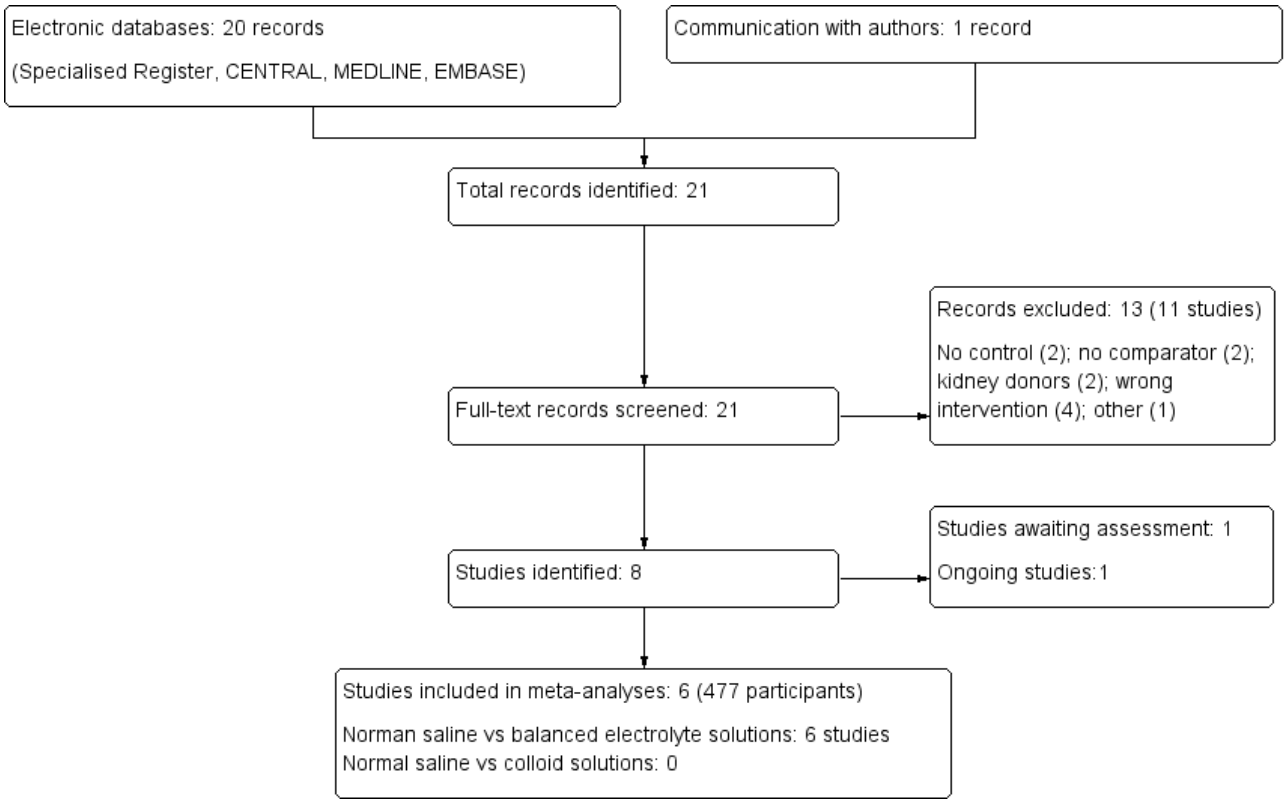
RESULTS

Description of studies

Results of the search

The process of study selection is outlined in Figure 1. We identified 20 potentially eligible citations through database searching and one through personal communication. Twenty-one citations (19 studies) were retrieved for full-text review. Cittanova 1996 and Pang 2011 each had two citations, one of which was a peer-reviewed journal article, and the other was a conference abstract. We excluded 11 studies after full-text review. One study (Nuraei 2010) is awaiting translation in order to be evaluated further, and one study is an RCT that is currently ongoing (ACTRN12612000023853). This left six studies for inclusion in the review. There were no disagreements between independent authors regarding any step of the review.

Figure 1. Study flow diagram



Included studies

Six studies (477 participants) were included in the review. Detailed descriptions of participant characteristics and study design are provided in the Characteristics of included studies table. O'Malley 2005 included both living and deceased-donor kidney transplant recipients, Potura 2015 included deceased-donor kidney transplant recipients only, and the remaining four studies included living-donor kidney transplant recipients only. Hadimioglu 2008 compared normal saline with lactated ringers solution and Plasma-lyte® in a three-arm design, Potura 2015 compared normal saline with the balanced electrolyte solution Elo-Mel isoton®, and the remainder compared normal saline with lactated ringers. Five out of six studies administered the study fluids during the intra-operative period only, and the remaining study (Potura 2015) continued the study fluid until discharge from the anaesthetic recovery room. Two studies administered buffered crystalloid solution to all patients in the post-operative period (Kim 2013; O'Malley 2005), and one study (Kim 2013) administered 5% albumin intra-operatively to all patients. There were no RCTs comparing normal saline to colloids, dextrose or dilutions of normal saline. Therefore, the only comparisons that were made were between balanced electrolyte solutions (lactated ringers solution, Plasma-lyte® and Elo-Mel isoton®) and normal saline.

Excluded studies

Eleven studies were excluded from the review: three studies had no normal saline control arm (Dai 2011; Dawidson 1987; Wu 2010), two studies were of kidney donors (Cittanova 1996; Mertens zur Borg 2008), three studies investigated different rates or volumes of fluid administration (Hatch 1985; Magpantay 2011; Othman 2010), the intervention was a pharmacological agent in two studies (Pang 2011; Starke 2012), and one study had no comparator arm (Abdallah 2014). Further information is provided in the Characteristics of excluded studies table.

Studies awaiting classification

Nuraei 2010 is a quasi-RCT comparing lactated ringers solution to normal saline in kidney transplant recipients. This study is awaiting translation in order to be classified.

Ongoing studies

ACTRN12612000023853 is an ongoing RCT comparing balanced electrolyte solutions to normal saline in adult kidney transplant recipients.

Risk of bias in included studies

A summary of the risk of bias assessment is provided in Figure 2 and Figure 3. The overall risk of bias was low for selection bias and unclear for the remaining domains.

Figure 2. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.

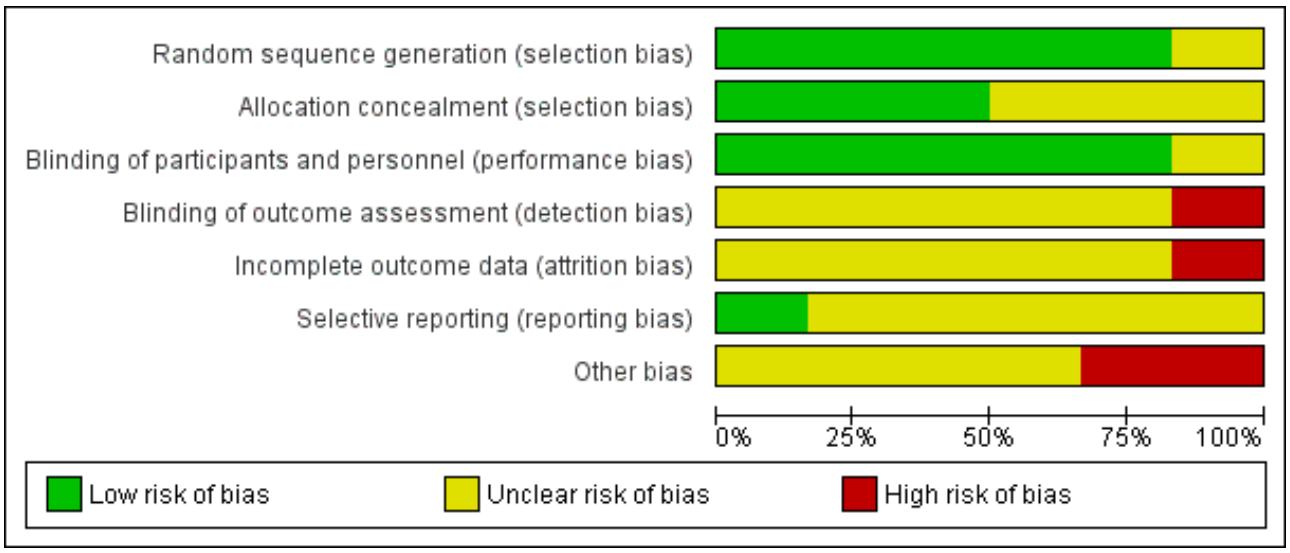
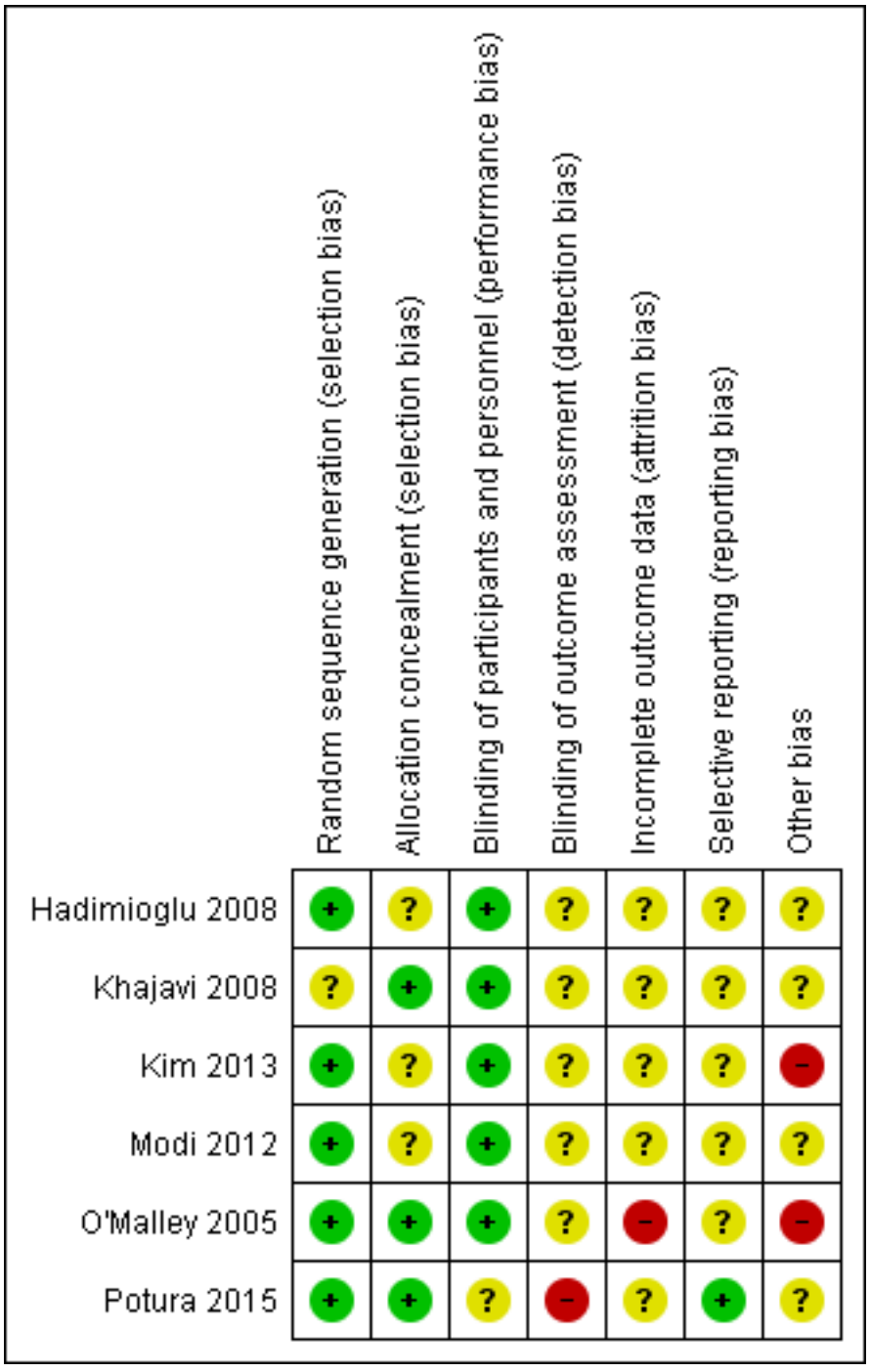


Figure 3. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.



Allocation

Five studies adequately performed and reported on random sequence generation (Hadimioglu 2008; Kim 2013; Modi 2012; O'Malley 2005; Potura 2015), with no information provided in the remaining study.

Three studies (Khajavi 2008; O'Malley 2005; Potura 2015) reported adequate allocation concealment techniques, with no information provided in the remaining three studies.

Blinding

Five studies reported on blinding for clinicians and participants, which was achieved by covering fluid bags with opaque tape (O'Malley 2005, Khajavi 2008, Modi 2012), or by the preparation of unlabelled fluid bags (Hadimioglu 2008; Kim 2013). Potura 2015 did not report on blinding of clinicians and participants, and no study reported on blinding for outcome or data assessors.

Incomplete outcome data

Only one study reported on loss to follow-up (Potura 2015) and one study (Kim 2013) reported on dropout rate. The intention-to-treat principle was not adhered to in two studies; Potura 2015 excluded two patients from the balanced electrolyte solutions arm after randomisation due to "unsuitable vessels", and O'Malley 2005 excluded three patients after randomisation due to pre-operative hyperkalaemia. No further information on these three patients was provided, including which groups they were randomised to. In the remaining four studies there was no information on whether or not intention-to-treat analysis was used.

Selective reporting

Selective reporting was unclear for the majority of studies. Potura 2015 was the only study registered with a clinical trials registry with a study protocol describing outcomes. The outcomes in the protocol were the same as the published study. The remaining studies did not have a protocol to assessment selective reporting.

Other potential sources of bias

Kim 2013 and O'Malley 2005 administered a buffered crystalloid solution to all patients in the post-operative period, exposing the control group to a balanced electrolyte solution. Potura 2015 was the only study with a conflict of interest declaration and reported no industry sources of funding. The remaining studies did not provide information on funding sources.

Effects of interventions

Primary outcomes

Delayed graft function

Three studies reported on delayed graft function (Hadimioglu 2008; Kim 2013; Potura 2015). There was no difference in the risk of delayed graft function between participants receiving intra-operative balanced electrolyte solutions compared with normal saline (Analysis 1.1 (3 studies, 298 participants): RR 1.03, 95% CI 0.62 to 1.70; I^2 = 0%).

Hyperkalaemia

Two studies reported on hyperkalaemia (O'Malley 2005; Potura 2015). There was no difference in the risk of hyperkalaemia in patients receiving balanced electrolyte solutions compared to normal saline (Analysis 1.2 (2 studies, 199 participants): RR 0.48, 95% CI 0.04 to 6.10). There was moderate heterogeneity for this outcome (I^2 = 69%).

Secondary outcomes

Acid-base status

Three studies reported pH at end of surgery (Hadimioglu 2008; Khajavi 2008; O'Malley 2005). The mean blood pH was an average of 0.07 units higher in patients who received balanced electrolyte solutions compared to normal saline (Analysis 1.3 (3 studies, 193 participants): MD 0.07 units, 95% CI 0.05 to 0.09; I^2 = 9%).

Three studies reported serum bicarbonate at the end of surgery (Hadimioglu 2008; Modi 2012; O'Malley 2005). The mean serum bicarbonate was 3.02 mEq/L higher in the balanced electrolyte solutions group compared to the normal saline group (Analysis 1.4; (3 studies, 215 participants): MD 3.02 mEq/L, 95% CI 2.00 to 4.05; I^2 = 21%).

Patients who received balanced electrolyte solutions had a mean chloride concentration 9.93 mmol/L lower at the end of surgery compared to the normal saline group (Analysis 1.5 (3 studies, 215 participants): MD -9.93 mmol/L, 95% CI -19.96 to 0.11) (Hadimioglu 2008; Modi 2012; O'Malley 2005). Heterogeneity was high (I^2 = 99%)

Four studies reported serum potassium at the end of surgery (Hadimioglu 2008; Khajavi 2008; Modi 2012; O'Malley 2005). There was no difference serum potassium in those who received balanced electrolyte solutions compared to normal saline (Analysis 1.6 (4 studies, 267 participants): MD -0.24 mmol/L, 95% CI -0.51 to 0.04). Heterogeneity was again high for this outcome (I^2 = 70%).

Adverse events

Adverse events were reported by two studies. O'Malley 2005 reported graft loss in two patients from the normal saline group and one patient from the balanced electrolyte solutions group; however the timeframe for this loss was not reported. In addition, four episodes of biopsy-proven acute rejection in the normal saline group and two in the balanced electrolyte solutions group were reported in this study. Khajavi 2008 reported two patients with acute renal artery thrombosis in the balanced electrolyte solutions group and none in the normal saline group.

Subgroup analysis

We performed subgroup analysis for living-donor kidney transplant recipients for the outcome of delayed graft function; however this did not substantially alter the pooled result (data not shown). Subgroup analysis was not performed for the remaining pre-specified groups or outcomes due to the small number of studies and events and the lack of data on these subgroups. In particular, there was only one study of deceased-donor kidney transplant recipients.

Sensitivity analysis

Exclusion of studies that administered buffered normal saline solutions to all patients in the post-operative period (Kim 2013; O'Malley 2005) resulted in a significantly lower mean serum potassium in the balanced electrolyte solutions group compared to the normal saline group (MD -0.33 mmol/L, 95% CI -0.65 to -0.01). We were unable to perform sensitivity analysis for the outcome of delayed graft function and hyperkalaemia due to the small study numbers, and further sensitivity analyses for the remaining outcomes did not change the magnitude or direction of effect.

DISCUSSION

Summary of main results

Intra-operative balanced electrolyte solutions were associated with a higher pH and bicarbonate level, and lower chloride concentration at the end of surgery compared to normal saline in patients undergoing kidney transplantation. There was no significant difference in the risk of delayed graft function or hyperkalaemia, and no difference in the mean serum potassium concentration between groups. These findings support the view that normal saline is associated with more hyperchloraemic metabolic acidosis than balanced electrolyte solutions; however the implications of this on clinical outcomes remain unclear.

Overall completeness and applicability of evidence

Nearly 70% of all participants included in this review underwent living-donor kidney transplantation, and 98% of deceased-donor transplant participants were included from one study (Potura 2015). Recipients of live-donor kidneys are at low risk for delayed graft function because the main determinants of this are cold ischaemia time and donor age, which are usually optimised in the live-donor setting. Since delayed graft function occurs less frequently in live- compared to deceased-donor transplantation, there may be potential for a greater magnitude of effect to be seen in deceased-donor transplant recipients, who represent a more high-risk group. Nevertheless, even in this high risk group, no difference in the risk of delayed graft function was demonstrated in this review. This may be because other factors such as ischaemic time and donor age are stronger determinants of delayed graft function, and play a more important role than the type of intra-operative fluid used. Subgroup analysis stratifying for delayed graft function risk would be useful to examine whether the choice of intra-operative fluids might be more important in higher risk groups.

The available evidence assessed the impact of intravenous fluids in the intra-operative setting only, a period that typically lasts two to four hours. However, during the immediate 48 to 72 hours post-transplantation, large volumes of intravenous fluid are commonly administered to transplant recipients. Clinical outcomes of delayed graft function, hyperkalaemia and acid-base status are therefore likely to be affected by the choice of post-operative as well as intra-operative fluids, and studies that assess post-operative intravenous fluid choice during kidney transplant are required.

Individual studies described the administration of intra-operative fluids to achieve a target central venous pressure, however, no study reported on the total volume of fluid delivered to study participants. The total volume of fluid is likely to influence the total chloride load and the development of hyperchloraemic metabolic acidosis, and may account for some of the heterogeneity seen. Future studies addressing this question should report on total fluid volume delivered.

Quality of the evidence

The overall quality of evidence included in this review was low to moderate. Randomisation and blinding of the included studies was adequate overall, however the reporting of important outcomes such as delayed graft function and hyperkalaemia was poor and could introduce reporting bias into this review. The low adverse event rates may reflect under-reporting of these outcomes, although serious adverse events such as death or graft failure are uncommon in living-donor transplant recipients, who were the majority of the review participants. The duration of follow-up for all included studies was very short, and ranged from one day to six months post-surgery. This did not allow for any assessment of long-term clinical outcomes such as graft failure or patient survival.

Two of the studies in this review (Kim 2013; O'Malley 2005) administered buffered crystalloid solutions to all patients in the post-operative period in the form of a dilution of normal saline with bicarbonate added. This may have diminished any effect of hyperchloraemic metabolic acidosis in the normal saline group, causing the pH, bicarbonate, chloride and potassium levels to be more similar between the two groups, and potentially leading to a bias towards the null. However, given that the time point for acid-base measurements did not go beyond the end of surgery, it is unclear how these post-operative buffered solutions might bias results. Nevertheless, when sensitivity analysis was performed excluding these studies, the magnitude of effect for mean difference in serum potassium between the two groups increased, and became significant in favour of balanced electrolyte solutions. This may also explain some of the heterogeneity seen in the analysis of serum potassium and chloride concentrations at the end of surgery.

Potential biases in the review process

Meta-analysis remains retrospective research that is subject to the risks of bias of the included studies. The main limitation of this review is the low number of studies identified, and the resultant small sample size and low event rate. Significant publication bias cannot be excluded and is difficult to assess due to the small number of studies. In addition we were unable to translate one study (Nuraei 2010) in order to assess it for eligibility. However, we minimised the likelihood of bias by developing a detailed protocol prior to commencing this study, performing a meticulous and exhaustive search for published studies, and utilising explicit methodology for study selection, data extraction and data analysis.

Agreements and disagreements with other studies or reviews

This is the only systematic review to our knowledge that examines the effect of balanced electrolyte solutions compared to normal saline on clinically relevant outcomes in kidney transplant recipients. It agrees with recent reviews in the peri-operative and critical care settings that report an association between normal saline and hyperchloraemic metabolic acidosis (Krajewski 2014; Myburgh 2013) without an increase in clinically important adverse effects (Krajewski 2014).

AUTHORS' CONCLUSIONS

Implications for practice

Intra-operative administration of balanced electrolyte solutions compared to normal saline is associated with less hyperchloraemic metabolic acidosis in kidney transplant recipients. Therefore, use of these solutions should be considered in patients at high risk of metabolic acidosis. However it remains uncertain whether lower-chloride solutions lead to improved graft outcomes compared to normal saline.

Implications for research

The current data mainly reflect live-donor kidney transplant recipients, whereas the risk of delayed graft function is most relevant to the deceased-donor kidney transplant population. High-quality studies that assess deceased-donor kidney transplant recipients are therefore required. In addition, further studies should evaluate intravenous fluids delivered during the post-operative as well as intra-operative period, and report on total volume of fluid delivered, while assessing clinically important outcomes such as delayed graft function and hyperkalaemia.

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Khajavi 2008 *{published data only}*

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Magpantay 2011 *{published data only}*

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CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Hadimioglu 2008

Methods	• Study design: RCT • Study duration: not reported • Study follow-up period: to postoperative day 7
Participants	• Country: Turkey • Setting: University teaching hospital • Relevant health status: adult living-donor kidney transplant recipients • Number: treatment group (60); control group (30) • Mean age ± SD (years): treatment group (47 ± 12); control group (44 ± 13) • Sex (M/F): not reported • Cold ischaemia time (minutes): treatment group (33 ± 7); control group (32 ± 8) • Warm ischaemia time (minutes): treatment group (31 ± 7); control group (29 ± 8) • Exclusion criteria: severe cardiovascular disease; liver dysfunction; cadaveric kidney transplantation; diabetes; serum potassium level > 5.5 mmol/L

Interventions	Treatment group
	• Lactated ringers or Plasma-lyte®
	  * Intraoperative IV fluid at rate of 20 to 30 mL/kg/h to maintain CVP at 12 to 15 mm Hg
	Control group
	• Normal saline
	  * Intraoperative IV fluid at rate of 20 to 30 mL/kg/h to maintain CVP at 12 to 15 mm Hg
	Post-operative fluid
	• 5% dextrose with 0.45% saline
	Baseline immunosuppression
	• Induction: methylprednisolone 500 mg
	• Maintenance: all had same postoperative immunosuppressive protocol but no details given

Outcomes	• Delayed graft function: requirement for dialysis within 7 days post-transplant • Acid-base: mean difference in blood pH, serum potassium concentration, serum chloride concentration, and serum bicarbonate concentration at the end of surgery compared to baseline
Notes	• Funding source: no information on funding sources was provided
Risk of bias	

Hadimioglu 2008 *(Continued)*

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"A computer randomization program was used for patient group assignments." Page 264, paragraph 4
Allocation concealment (selection bias)	Unclear risk	Information on allocation concealment was not reported
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"The study solutions were prepared in unlabeled bags by the hospital pharmacy. Patients and clinicians were blinded to group assignments." Page 264, paragraph 4
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Specific information on masking of outcome and data assessors was not reported
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	No information on intention-to-treat principle or missing outcome data reported
Selective reporting (reporting bias)	Unclear risk	No trial registration or published protocol
Other bias	Unclear risk	No information on funding reported

Khajavi 2008

Methods	• Study design: RCT • Study duration: not reported • Study follow-up period: to postoperative day 3
Participants	• Country: Iran • Setting: university teaching hospital • Relevant health status: adult live-donor kidney transplant recipients • Number: treatment group (26); control group (26) • Mean age ± SD (years): treatment group (37 ± 13); control group (40 ± 14) • Sex (M/F): not reported • Cold ischaemia time (minutes): not reported • Warm ischaemia time (minutes): treatment group (4 ± 101); control group (5 ± 1) • Exclusion criteria: serum potassium level > 6.0 mEq/L

Interventions	Treatment group
	• Lactated ringers
	  * Intraoperative IV fluid at volume of 60 mL/kg titrated to keep CVP at 10 to 15 mm Hg
	Control group
	• Normal saline
	  * Intraoperative IV fluid at volume of 60 mL/kg titrated to keep CVP at 10 to 15 mm Hg
	Post-operative fluid
	• not reported

Khajavi 2008 *(Continued)*

	Baseline immunosuppression
	• Induction: not reported
	• Maintenance
	  * Prednisolone
	  * Cyclosporine
	  * Mycophenolate mofetil

Outcomes	• Acid-base status: mean difference in blood pH, serum potassium concentration, serum chloride concentration, and serum bicarbonate concentration at the end of surgery compared to baseline • Adverse events * Immediate renal artery thrombosis: treatment group (2); control group (0)
Notes	• Funding source: no information on funding sources was provided

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No information on random sequence generation was reported
Allocation concealment (selection bias)	Low risk	"Randomization was achieved using sealed envelopes." Page 536, paragraph 2
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"The fluid bags were covered with tape so that the personnel and clinicians do not have any idea of the type of the fluid administered." Page 536, paragraph 6
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Specific information on masking of outcome and data assessors was not reported
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	No information on intention-to-treat principle or missing outcome date reported
Selective reporting (reporting bias)	Unclear risk	No trial registration or published protocol
Other bias	Unclear risk	No information on funding reported

Kim 2013

Methods	• Study design: RCT • Study duration: August 2011 to April 2012 • Study follow-up period: to postoperative day 7
Participants	• Country: Republic of Korea • Setting: university teaching hospital • Relevant health status: adult live-donor kidney transplant recipients • Number: treatment group (30); control group (30) • Mean age ± SD (years): treatment group (44 ± 12); control group (46 ± 12) • Sex (M/F): treatment group (17/13); control group (21/9)

Kim 2013 *(Continued)*

- Cold ischaemia time (minutes): treatment group (74 ± 16); control group (80 ± 20)
- Warm ischaemia time (minutes): treatment group (35 ± 6); control group (36 ± 6)
- Exclusion criteria: severe cardiovascular or respiratory disease

Interventions	Treatment group
	• Plasma-lyte®
	  * Intraoperative IV fluid titrated to keep CVP at 12 to 15 mm Hg
	Control group
	• Normal saline
	  * Intraoperative IV fluid titrated to keep CVP at 12 to 15 mm Hg
	Co-intervention
	• 750 mL of intraoperative 5% albumin given to all participants
	Post-operative fluid
	• 0.45% saline with 5 mmol/L potassium chloride and 7 mmol/L bicarbonate
	Baseline immunosuppression
	• Induction: basiliximab and methylprednisolone
	• Maintenance
	  * Prednisolone
	  * Cyclosporin or tacrolimus
	  * Mycophenolic acid or mizoribine

Outcomes	• Delayed graft function: requirement for dialysis within 7 days post-transplant • Acid-base status: mean difference in blood pH, serum chloride concentration, and serum bicarbonate concentration at the end of surgery compared to baseline
Notes	• Funding source: no information on funding sources was provided

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"One day before transplant surgery, patients were assigned to either the NS group or the Plasmalyte group according to a random number sequence." Page 2192, paragraph 3
Allocation concealment (selection bias)	Unclear risk	Information on allocation concealment was not reported
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"The study solutions were prepared in unlabeled bags by a staff nurse who was not involved in the study. Attending anesthesiologists and surgeons were blinded to group assignments." Page 2191, paragraph 3
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Specific information on masking of outcome and data assessors was not reported
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	No information on intention-to-treat principle or missing outcome date reported. However, there were no drop-outs from the study

Kim 2013 *(Continued)*

Selective reporting (reporting bias)	Unclear risk	No trial registration or published protocol
Other bias	High risk	All patients received intra-operative albumin 5% as well as postoperative 0.45% normal saline with 5 mmol/L KCl and 7 mmol/L HCO_3. This could lead to non-differential misclassification error as the control group was also exposed to a balanced electrolyte solution. No information on funding reported

Modi 2012

Methods	• Study design: RCT • Study duration: not reported • Study follow-up period: to postoperative day 1
Participants	• Country: India • Setting: private research institute associated hospital • Relevant health status: adult live-donor kidney transplant recipients • Number: treatment group (37); control group (37) • Mean age ± SD (years): not reported • Sex (M/F): not reported • Cold ischaemia time (minutes): not reported • Warm ischaemia time (minutes): not reported • Exclusion criteria: severe cardiovascular disease, liver dysfunction, diabetes mellitus, preoperative serum potassium level > 5.5 mEq/L

Interventions	Treatment group
	• Lactated ringers
	  * Intraoperative IV fluid titrated to keep CVP at 12 to 15 mm Hg
	Control group
	• Normal saline
	  * Intraoperative IV fluid titrated to keep CVP at 12 to 15 mm Hg
	Post-operative fluid
	• Not reported
	Baseline immunosuppression
	• Induction: methylprednisolone
	• Maintenance: not reported

Outcomes	• Acid-base status: mean difference in blood pH, serum chloride concentration, and serum bicarbonate concentration at the end of surgery compared to baseline
Notes	• Funding source: no information on funding sources was provided

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	"A computer randomization program was used for patient group assignments." Page 135, paragraph 2

Modi 2012 *(Continued)*

Allocation concealment (selection bias)	Unclear risk	Information on allocation concealment was not reported
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"The solutions were supplied by our hospital pharmacy after completely covering each bag with opaque tape to ensure blinding to study personnel and patients." Page 135, paragraph 2
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Specific information on masking of outcome and data assessors was not reported
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	No information on intention-to-treat principle or missing outcome date reported
Selective reporting (reporting bias)	Unclear risk	No trial registration or published protocol
Other bias	Unclear risk	Published as a letter to the editor only. No information on funding reported

O'Malley 2005

Methods	• Study design: RCT • Study duration: not reported • Study follow-up period: 6 months
Participants	• Country: USA • Setting: university teaching hospitals • Relevant health status: adult living and deceased-donor kidney transplant recipients • Number: treatment group (25); control group (26) • Mean age ± SD (years): treatment group (44 ± 11); control group (44 ± 13) • Sex (M/F): treatment group (15/10); control group (17/9) • Donor type (living/deceased): treatment group (23/2); control group (25/1) • Cold ischaemia time (minutes): not reported • Warm ischaemia time (minutes): treatment group (34 ± 9); control group (34 ± 13) • Exclusion criteria: age < 18 years, religious prohibition of receipt of blood products, serum potassium level > 5.5 mEq/L before surgery

Interventions	Treatment group
	• Lactated ringers
	  * Intraoperative fluid only
	  * Volume and rate at discretion of clinician
	Control group
	• Normal saline
	  * Intraoperative fluid only
	  * Volume and rate at discretion of clinician
	Post-operative fluid
	• 5% dextrose with 0.45% saline
	• 0.45% saline with 20 mEq bicarbonate

O'Malley 2005 *(Continued)*

	Baseline immunosuppression
	• Induction: not reported
	• Maintenance
	  * Tapering steroids
	  * Calcineurin inhibitor
	  * Mycophenolate mofetil or sirolimus

Outcomes	• Clinically significant hyperkalaemia: serum potassium concentration > 6.0 mEq/L
	• Acid-base status: mean difference in blood pH, serum chloride concentration, and serum bicarbonate concentration at the end of surgery compared to baseline
	• Adverse events
	  * Graft loss defined as requirement for dialysis (timeframe not specified): treatment group (1); control group (2)
	  * Biopsy proven acute rejection: treatment group (2); control group (4)

Notes	• Funding source: no information on funding sources was provided

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Randomization was achieved by computer generation of random number lists..." Page 1519, paragraph 2
Allocation concealment (selection bias)	Low risk	"Randomization was achieved by computer generation of random number lists, in blocks of four, and a closed envelope technique." Page 1519, paragraph 2
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"The investigational pharmacy completely covered each bag of study fluid with opaque tape to ensure blinding of all study personnel and clinicians to the fluid type." Page 1520, paragraph 1
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Specific information on masking of outcome and data assessors was not reported
Incomplete outcome data (attrition bias) All outcomes	High risk	The intention-to-treat principle was not adhered to. 54 patients were randomised and data from 51 patients were analysed. 3 patients were excluded after randomisation due to preoperative hyperkalaemia. Page 1520, paragraph 7
Selective reporting (reporting bias)	Unclear risk	No trial registration or published protocol
Other bias	High risk	All patients received 5% dextrose/0.45% normal saline with 20 mEq/L HCO_3. This could lead to non-differential misclassification error as the control group was also exposed to a balanced electrolyte solution. No information on funding reported

Potura 2015

Methods	• Study design: RCT • Study duration: June 2010 to February 2013

Potura 2015 *(Continued)*

	• Study follow-up period: to postoperative day 7
Participants	• Country: Austria • Setting: university teaching hospital • Relevant health status: adult deceased-donor kidney transplant recipients • Number: treatment group (74); control group (76) • Mean age ± SD (years): treatment group (54 ± 13); control group (56 ± 13) • Sex (M/F): treatment group (47/27); control group (48/28) • Cold ischaemia time (minutes): not reported • Warm ischaemia time (minutes): not reported • Exclusion criteria: age < 18 years, preoperative serum potassium level > 5.5 mmol/L

Interventions	Treatment group
	• Elo-Mel isoton®
	  * Intraoperative rate at 4 mL/kg/h
	  * Recovery room postoperative rate at 2 mL/kg/h
	Control group
	• Normal saline
	  * Intraoperative rate at 4 mL/kg/h
	  * Recovery room postoperative rate at 2 mL/kg/h
	Post-operative (ward) fluid
	• Not reported
	Baseline immunosuppression
	• Induction: not reported
	• Maintenance: not reported

Outcomes	• Delayed graft function: requirement for dialysis within 7 days post-transplant • Clinically significant hyperkalaemia: serum potassium level > 6.0 mmol/L • Acid-base status: fluctuation in serum potassium concentration, chloride concentration and base excess during surgery
Notes	• Funding source: the study had no funding

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Computer-based randomization was performed using sealed envelopes." Page 124, paragraph 4
Allocation concealment (selection bias)	Low risk	"Computer-based randomization was performed using sealed envelopes." Page 124, paragraph 4
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	"We chose to perform an open label study...the patient is already sedated before start of surgery and then is totally anesthetized." Page128, paragraph 4
Blinding of outcome assessment (detection bias) All outcomes	High risk	"We chose to perform an open label study..." Page128, paragraph 4

Potura 2015 *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	Unclear risk	The intention-to-treat principle was not adhered to. 74 patients randomised to the Balanced Solution group but only 72 patients analysed. 2 patients did not receive intervention due to "unsuitable vessel situation" (Page 126, Figure 1), however this is not discussed in the text further. It is unclear whether this infers that the transplant did not proceed for these 2 patients. There were no losses to follow-up
Selective reporting (reporting bias)	Low risk	The study was registered on clinicaltrials.gov with protocol outcomes the same as reported outcomes
Other bias	Unclear risk	Out of 397 eligible cadaveric transplants performed during the study period, only 150 recipients were included in the study and 247 excluded due to absence of study team personnel during those transplants. There was no information on any differences in characteristics between included and excluded transplant recipients making it difficult to assess selection bias due to this

CVP - central venous pressure; HCO_3 - bicarbonate; IV - intravenous; M/F - male/female; RCT - randomised controlled trial; SD - standard deviation

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Abdallah 2014	No comparator arm (both groups received normal saline)
Cittanova 1996	Intervention applied to kidney donors
Dai 2011	No normal saline control arm
Dawidson 1987	No comparator arm
Hatch 1985	Intervention compared different rates of fluid administration
Magpantay 2011	Intervention was not perioperative
Mertens zur Borg 2008	Intervention applied to kidney donors
Othman 2010	Intervention compared different rates of fluid administration
Pang 2011	Intervention was parecoxib
Starke 2012	Intervention was potassium citrate
Wu 2010	Intervention compared 2 different types of colloids and both arms received lactated ringers solution

Characteristics of studies awaiting assessment *[ordered by study ID]*

Nuraei 2010

Methods	Double-blind quasi-RCT
Participants	Adult live-donor kidney transplant recipients

Nuraei 2010 *(Continued)*

Interventions	Lactated ringers compared to normal saline
Outcomes	Acid-base parameters at the end of surgery
Notes	This study is awaiting translation in order to be classified

RCT - randomised controlled trial

Characteristics of ongoing studies *[ordered by study ID]*

ACTRN12612000023853

Trial name or title	Balanced fluid therapy and early kidney function in patients undergoing renal transplantation
Methods	RCT
Participants	Adult deceased-donor kidney transplant recipients
Interventions	Plasma-lyte® compared to normal saline
Outcomes	Hyperkalaemia and acid-base balance
Starting date	21-11-2012
Contact information	
Notes	

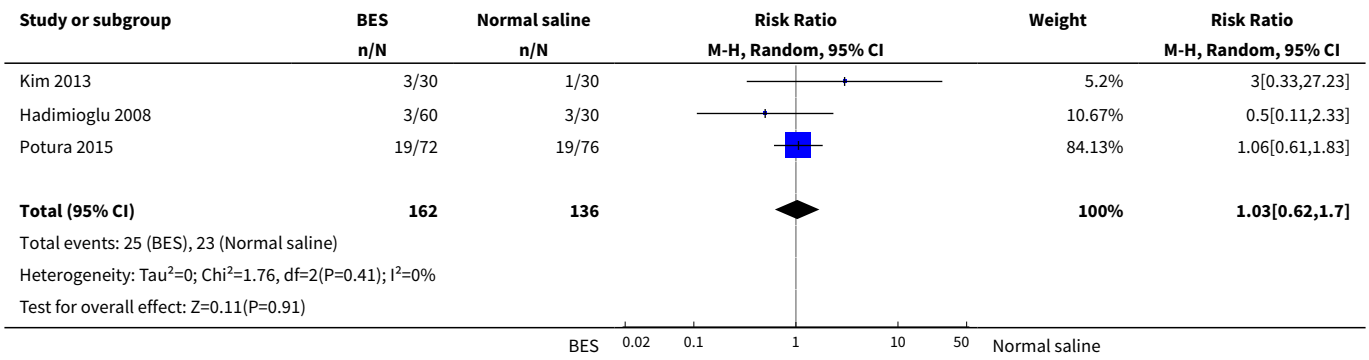
RCT - randomised controlled trial

DATA AND ANALYSES

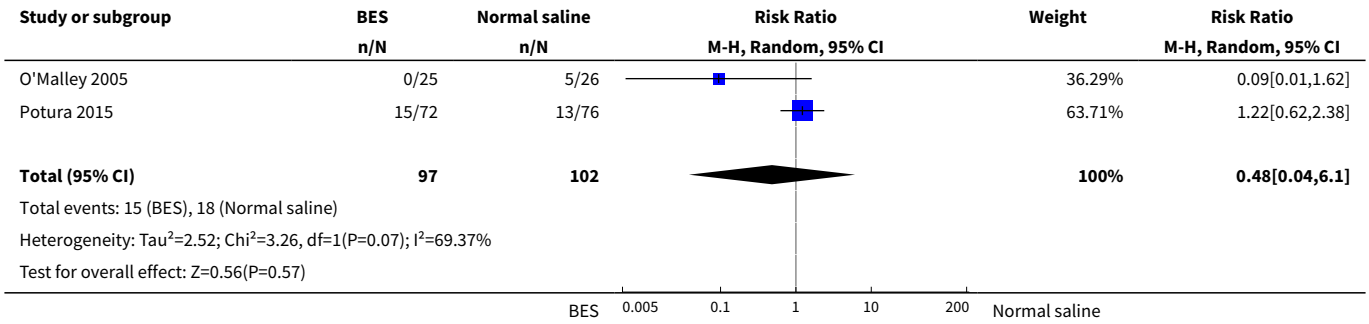
Comparison 1. Balanced electrolyte solutions versus normal saline

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Delayed graft function	3	298	Risk Ratio (M-H, Random, 95% CI)	1.03 [0.62, 1.70]
2 Hyperkalaemia	2	199	Risk Ratio (M-H, Random, 95% CI)	0.48 [0.04, 6.10]
3 Blood pH at end of surgery	3	193	Mean Difference (IV, Random, 95% CI)	0.07 [0.05, 0.09]
4 Serum bicarbonate at end of surgery	3	215	Mean Difference (IV, Random, 95% CI)	3.02 [2.00, 4.05]
5 Serum chloride at end of surgery	3	215	Mean Difference (IV, Random, 95% CI)	-9.93 [-19.96, 0.11]
6 Serum potassium at end of surgery	4	267	Mean Difference (IV, Random, 95% CI)	-0.24 [-0.51, 0.04]

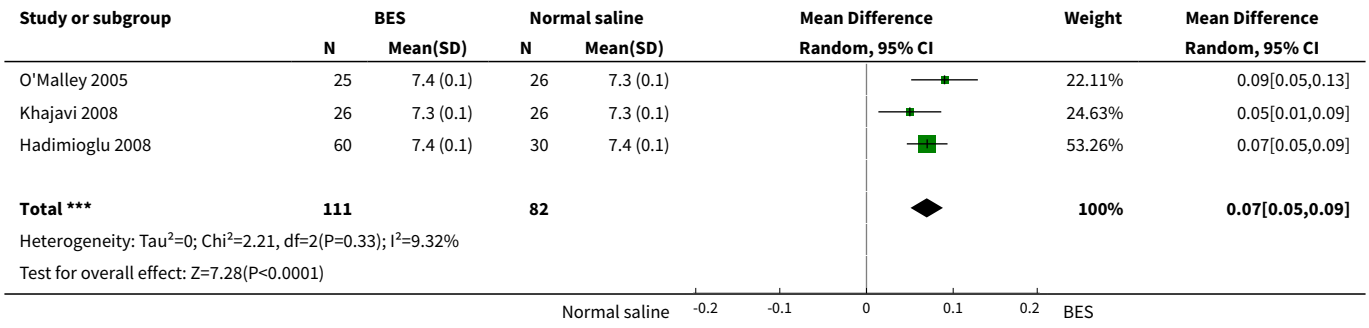
Analysis 1.1. Comparison 1 Balanced electrolyte solutions versus normal saline, Outcome 1 Delayed graft function.



Analysis 1.2. Comparison 1 Balanced electrolyte solutions versus normal saline, Outcome 2 Hyperkalaemia.

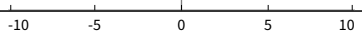


Analysis 1.3. Comparison 1 Balanced electrolyte solutions versus normal saline, Outcome 3 Blood pH at end of surgery.



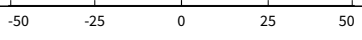
Analysis 1.4. Comparison 1 Balanced electrolyte solutions versus normal saline, Outcome 4 Serum bicarbonate at end of surgery.

Study or subgroup	BES N	BES Mean(SD)	Normal saline N	Normal saline Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
O'Malley 2005	25	21 (4)	26	18 (3)		23.6%	3[1.05,4.95]
Modi 2012	37	21.6 (3.6)	37	19.5 (3)		35.87%	2.15[0.65,3.65]
Hadimioglu 2008	60	22 (3.6)	30	18.2 (2.9)		40.53%	3.81[2.42,5.2]
Total ***	**122**		**93**			**100%**	**3.02[2,4.05]**
Heterogeneity: Tau²=0.17; Chi²=2.53, df=2(P=0.28); I²=20.93%							
Test for overall effect: Z=5.78(P<0.0001)							



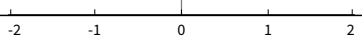
Analysis 1.5. Comparison 1 Balanced electrolyte solutions versus normal saline, Outcome 5 Serum chloride at end of surgery.

Study or subgroup	BES N	BES Mean(SD)	Normal saline N	Normal saline Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
O'Malley 2005	25	106 (4)	26	111 (4)		33.16%	-5[-7.2,-2.8]
Modi 2012	37	98.5 (3)	37	103.9 (4.3)		33.37%	-5.42[-7.11,-3.73]
Hadimioglu 2008	60	106.1 (1.8)	30	125.4 (3.7)		33.47%	-19.3[-20.7,-17.9]
Total ***	**122**		**93**			**100%**	**-9.93[-19.96,0.11]**
Heterogeneity: Tau²=77.82; Chi²=202.32, df=2(P<0.0001); I²=99.01%							
Test for overall effect: Z=1.94(P=0.05)							



Analysis 1.6. Comparison 1 Balanced electrolyte solutions versus normal saline, Outcome 6 Serum potassium at end of surgery.

Study or subgroup	BES N	BES Mean(SD)	Normal saline N	Normal saline Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
Khajavi 2008	26	4 (0.8)	26	4.7 (0.7)		20.26%	-0.7[-1.11,-0.29]
O'Malley 2005	25	4.6 (0.6)	26	4.5 (0.8)		21.25%	0.1[-0.29,0.49]
Modi 2012	37	4 (0.7)	37	4.3 (0.6)		25.78%	-0.32[-0.62,-0.02]
Hadimioglu 2008	60	3.8 (0.3)	30	3.9 (0.4)		32.71%	-0.1[-0.27,0.07]
Total ***	**148**		**119**			**100%**	**-0.24[-0.51,0.04]**
Heterogeneity: Tau²=0.05; Chi²=9.98, df=3(P=0.02); I²=69.93%							
Test for overall effect: Z=1.7(P=0.09)							



ADDITIONAL TABLES

Table 1. Electrolyte content of common fluids

	Crystalloids						
		Lower-chloride solutions					
			Balanced electrolyte solutions			Colloids	
	Normal (0.9%) saline	Dextrose 5%	Plasma-Lyte ®	Elo-Mel isoton ®	CSL/Ringer's lactate	Albumin 4%	Gelatins
Na^+ (mmol/L)	154	0	140	140	131	140	145
K^+ (mmol/L)	0	0	5	5	4-5	0	4-5
Cl^- (mmol/L)	154	0	98	108	112	128	120-145
HCO_3^- (mmol/L)	0	0	50 (27 as acetate, 23 as gluconate)	45 (as acetate)	28 (as lactate)	0	0
Osmolarity (mOsm/L)	310	252	297	302	255	250	284

Na^+ - sodium concentration; Cl^- - chloride concentration; CSL - compound sodium lactate; HCO_3^- - bicarbonate concentration; K^+ - potassium concentration

APPENDICES

Appendix 1. Electronic search strategies

Database	Search terms
CENTRAL	1. MeSH descriptor Kidney Transplantation, this term only 2. MeSH descriptor Isotonic Solutions, this term only 3. MeSH descriptor Sodium Chloride, this term only 4. MeSH descriptor Fluid Therapy, this term only 5. MeSH descriptor Acid-Base Equilibrium, this term only 6. (saline*):ti,ab,kw in Trials 7. (sodium chloride*):ti,ab,kw in Trials 8. (lactated ringer*):ti,ab,kw in Trials 9. (hartmann*):ti,ab,kw in Trials 10.(plasmalyte):ti,ab,kw in Trials 11.(#2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10) 12.(#1 AND #11)
MEDLINE (OVID SP)	1. Kidney Transplantation/ 2. Isotonic Solutions/ 3. Sodium Chloride/ 4. Fluid Therapy/ 5. saline.tw. 6. sodium chloride.tw. 7. lactated ringer$.tw. 8. hartmann$.tw. 9. plasmalyte.tw. 10.Acid-Base Equilibrium/ 11.or/2-10 12.and/1,11
EMBASE	1. exp kidney transplantation/ 2. sodium chloride/ 3. isotonic solution/ 4. acid base balance/ 5. saline.tw. 6. hartmann$.tw. 7. lactated ringer$.tw. 8. plasmalyte.tw. 9. sodium chloride.tw. 10.or/2-9 11.and/1,10

Appendix 2. Risk of bias assessment tool

Potential source of bias	Assessment criteria

(Continued)

Random sequence generation Selection bias (biased allocation to interventions) due to inadequate generation of a randomised sequence	*Low risk of bias:* Random number table; computer random number generator; coin tossing; shuffling cards or envelopes; throwing dice; drawing of lots; minimization (minimization may be implemented without a random element, and this is considered to be equivalent to being random).
	High risk of bias: Sequence generated by odd or even date of birth; date (or day) of admission; sequence generated by hospital or clinic record number; allocation by judgement of the clinician; by preference of the participant; based on the results of a laboratory test or a series of tests; by availability of the intervention.
	Unclear: Insufficient information about the sequence generation process to permit judgement.
Allocation concealment Selection bias (biased allocation to interventions) due to inadequate concealment of allocations prior to assignment	*Low risk of bias:* Randomisation method described that would not allow investigator/participant to know or influence intervention group before eligible participant entered in the study (e.g. central allocation, including telephone, web-based, and pharmacy-controlled, randomisation; sequentially numbered drug containers of identical appearance; sequentially numbered, opaque, sealed envelopes).
	High risk of bias: Using an open random allocation schedule (e.g. a list of random numbers); assignment envelopes were used without appropriate safeguards (e.g. if envelopes were unsealed or non-opaque or not sequentially numbered); alternation or rotation; date of birth; case record number; any other explicitly unconcealed procedure.
	Unclear: Randomisation stated but no information on method used is available.
Blinding of participants and personnel Performance bias due to knowledge of the allocated interventions by participants and personnel during the study	*Low risk of bias*: No blinding or incomplete blinding, but the review authors judge that the outcome is not likely to be influenced by lack of blinding; blinding of participants and key study personnel ensured, and unlikely that the blinding could have been broken.
	High risk of bias: No blinding or incomplete blinding, and the outcome is likely to be influenced by lack of blinding; blinding of key study participants and personnel attempted, but likely that the blinding could have been broken, and the outcome is likely to be influenced by lack of blinding.
	Unclear: Insufficient information to permit judgement
Blinding of outcome assessment Detection bias due to knowledge of the allocated interventions by outcome assessors.	*Low risk of bias:* No blinding of outcome assessment, but the review authors judge that the outcome measurement is not likely to be influenced by lack of blinding; blinding of outcome assessment ensured, and unlikely that the blinding could have been broken.
	High risk of bias: No blinding of outcome assessment, and the outcome measurement is likely to be influenced by lack of blinding; blinding of outcome assessment, but likely that the blinding could have been broken, and the outcome measurement is likely to be influenced by lack of blinding.
	Unclear: Insufficient information to permit judgement
Incomplete outcome data Attrition bias due to amount, nature or handling of incomplete outcome data.	*Low risk of bias:* No missing outcome data; reasons for missing outcome data unlikely to be related to true outcome (for survival data, censoring unlikely to be introducing bias); missing outcome data balanced in numbers across intervention groups, with similar reasons for missing data across groups; for dichotomous outcome data, the proportion of missing outcomes compared with observed event risk not enough to have a clinically relevant impact on the intervention effect estimate; for continuous outcome data, plausible effect size (difference in means or standardized difference in means) among missing outcomes not enough to have a clinically relevant impact on observed effect size; missing data have been imputed using appropriate methods.
	High risk of bias: Reason for missing outcome data likely to be related to true outcome, with either imbalance in numbers or reasons for missing data across intervention groups; for dichotomous outcome data, the proportion of missing outcomes compared with observed event risk enough to induce clinically relevant bias in intervention effect estimate; for continuous outcome data, plausible effect size (difference in means or standardized difference in means) among missing outcomes enough to induce clinically relevant bias in observed effect size; 'as-treated' analysis done with

(Continued)

	substantial departure of the intervention received from that assigned at randomisation; potentially inappropriate application of simple imputation.
	Unclear: Insufficient information to permit judgement
Selective reporting Reporting bias due to selective outcome reporting	*Low risk of bias:* The study protocol is available and all of the study's pre-specified (primary and secondary) outcomes that are of interest in the review have been reported in the pre-specified way; the study protocol is not available but it is clear that the published reports include all expected outcomes, including those that were pre-specified (convincing text of this nature may be uncommon).
	High risk of bias: Not all of the study's pre-specified primary outcomes have been reported; one or more primary outcomes is reported using measurements, analysis methods or subsets of the data (e.g. subscales) that were not pre-specified; one or more reported primary outcomes were not pre-specified (unless clear justification for their reporting is provided, such as an unexpected adverse effect); one or more outcomes of interest in the review are reported incompletely so that they cannot be entered in a meta-analysis; the study report fails to include results for a key outcome that would be expected to have been reported for such a study.
	Unclear: Insufficient information to permit judgement
Other bias Bias due to problems not covered elsewhere in the table	*Low risk of bias:* The study appears to be free of other sources of bias.
	High risk of bias: Had a potential source of bias related to the specific study design used; stopped early due to some data-dependent process (including a formal-stopping rule); had extreme baseline imbalance; has been claimed to have been fraudulent; had some other problem.
	Unclear: Insufficient information to assess whether an important risk of bias exists; insufficient rationale or evidence that an identified problem will introduce bias.

CONTRIBUTIONS OF AUTHORS

1. Draft the protocol: SW, PM, MR
2. Study selection: SW, PM
3. Extract data from studies: SW, PM
4. Enter data into RevMan: SW
5. Carry out the analysis: SW, PM, MR
6. Interpret the analysis: SW, PM, MR
7. Draft the final review: SW, PM, MR
8. Disagreement resolution: MR
9. Update the review: SW

DECLARATIONS OF INTEREST

- Susan Wan: none known
- Matthew A Roberts: I have received competitive research funding and speaker's honoraria for research in subjects not related to this current Cochrane Review
- Peter Mount: is an investigator in an investigator initiated ongoing study entitled "Balanced fluid therapy and early kidney function in patients undergoing renal transplantation" (ACTRN12612000023853). The fluids used in this study are provided for and paid for by Baxter Healthcare.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

1. Secondary outcomes
   - We intended to examine acid-base status at the end of surgery compared to baseline and at day three compared to baseline. However, no studies reported on acid-base status at day three, therefore only the comparison between end of surgery and baseline was made.
2. Assessment of reporting bias
   - We intended to use funnel plots to assess reporting bias, however this was not possible due to the small number of studies identified.

INDEX TERMS

Medical Subject Headings (MeSH)

*Delayed Graft Function [blood]; *Hyperkalemia [blood] [chemically induced]; *Kidney Transplantation; Gluconates [pharmacology]; Hydrogen-Ion Concentration; Infusions, Intravenous; Isotonic Solutions [pharmacology]; Kidney [*drug effects]; Magnesium Chloride [pharmacology]; Potassium Chloride [pharmacology]; Ringer's Solution; Sodium Acetate [pharmacology]; Sodium Chloride [adverse effects] [chemistry] [*pharmacology]; Solutions

MeSH check words

Adult; Humans