Systematic review

Meta-analysis of high- *versus* low-chloride content in perioperative and critical care fluid resuscitation

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Background: **The objective of this systematic review and meta-analysis was to assess the relationship between the chloride content of intravenous resuscitation fluids and patient outcomes in the perioperative or intensive care setting.**

Methods: **Systematic searches were performed of PubMed/MEDLINE, Embase and Cochrane Library (CENTRAL) databases in accordance with PRISMA guidelines. Randomized clinical trials, controlled clinical trials and observational studies were included if they compared outcomes in acutely ill or surgical patients receiving either high-chloride (ion concentration greater than 111 mmol/l up to and including 154 mmol/l) or lower-chloride (concentration 111 mmol/l or less) crystalloids for resuscitation. Endpoints examined were mortality, measures of kidney function, serum chloride, hyperchloraemia/metabolic acidosis, blood transfusion volume, mechanical ventilation time, and length of hospital and intensive care unit stay. Risk ratios (RRs), mean differences (MDs) or standardized mean differences (SMDs) and confidence intervals were calculated using fixed-effect modelling.**

Results: **The search identified 21 studies involving 6253 patients. High-chloride fluids did not affect mortality but were associated with a significantly higher risk of acute kidney injury (RR 1·64, 95 per cent c.i. 1·27 to 2·13; $P < 0·001$) and hyperchloraemia/metabolic acidosis (RR 2·87, 1·95 to 4·21; $P < 0·001$). High-chloride fluids were also associated with greater serum chloride (MD 3·70 (95 per cent c.i. 3·36 to 4·04) mmol/l; $P < 0·001$), blood transfusion volume (SMD 0·35, 0·07 to 0·63; $P = 0·014$) and mechanical ventilation time (SMD 0·15, 0·08 to 0·23; $P < 0·001$). Sensitivity analyses excluding heavily weighted studies resulted in non-statistically significant effects for acute kidney injury and mechanical ventilation time.**

Conclusion: **A weak but significant association between higher chloride content fluids and unfavourable outcomes was found, but mortality was unaffected by chloride content.**

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Introduction

The administration of intravenous fluids for resuscitation occurs routinely in the perioperative setting and in the management of critically ill patients. There has been considerable interest in defining optimal fluid resuscitation strategies[1], yet practice patterns and fluid selection vary considerably[2]. While much attention has been directed at the 'colloid *versus* crystalloid' debate, increasing evidence suggests clinically important differences related to intravenous fluid chloride content[3–7].

Often referred to as 'normal saline', 0·9 per cent saline contains sodium and chloride in supraphysiological concentrations. Balanced solutions, in contrast, contain significantly lower concentrations of sodium and chloride, making them closer in composition to plasma than 0·9 per cent saline[6]. Despite a lack of evidence supporting the superiority of 0·9 per cent saline[7], it is commonly used as a resuscitation fluid and has generally served as the 'control fluid' in large trials[8,9]. Administration of 0·9 per cent saline causes hyperchloraemic metabolic acidosis[10–15], and consequently some guidelines recommend the use of balanced solutions as a default during resuscitation[16]. Hyperchloraemia has also been associated with decreased renal perfusion[17–21], impaired immune function[22–24] and

mortality[25], suggesting that hyperchloraemia may have clinically relevant effects.

Studies[26,27] have examined differences between groups treated with high-chloride *versus* low-chloride solutions, and a Cochrane systematic review[28] of randomized controlled trials (RCTs) examined clinical outcomes following the perioperative use of buffered *versus* non-buffered fluids. A recent systematic review[29] of prospective RCTs evaluated the impact of near-isotonic or isotonic crystalloids on acid–base status and other physiological, haemodynamic and clinical outcomes. However, no analyses have focused specifically on the chloride content of crystalloids administered for resuscitation in the broader context of both perioperative and critical care medicine. Therefore, a systematic review and meta-analysis was conducted to determine whether the chloride content of resuscitation fluids used in the operating theatre or intensive care unit (ICU) setting is associated with differences in outcomes.

Methods

Study selection

Approval for the study was obtained from the Duke University Institutional Review Board on 7 August 2013. In accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement[30], systematic searches of the PubMed/MEDLINE, Embase and Cochrane Central Register of Controlled Trials Library (CENTRAL) databases were carried out using predefined search terms that addressed study design, intervention and intravenous fluid type (*Appendix S1*, supporting information). These were supplemented by manual searches by the investigators in order to capture as much of the literature as possible. Searches were limited to published English-language studies in human subjects, covering all dates up to and including 22 August 2013. Unique articles were screened based on their title/abstract, and studies requiring full review were identified.

Inclusion in the meta-analysis required that a given study meet the following criteria: comparison of an isotonic crystalloid fluid characterized by a supraphysiological chloride concentration (ion concentration greater than 111 mmol/l up to and including 154 mmol/l, for example 0·9 per cent saline) with a near-isotonic or isotonic crystalloid fluid characterized by a near-physiological chloride concentration (ion concentration 111 mmol/l or less, for example Ringer's lactate), given intravenously for the purpose of fluid resuscitation or replacement; comparison in either acutely ill patients in the ICU or surgical patients in the perioperative period; and evaluation of at least one of the following endpoints: mortality, acute kidney injury (AKI)/renal failure (including use of dialysis), hospital length of stay (LOS), ICU LOS, hyperchloraemia/metabolic acidosis, serum creatinine, serum chloride, urine output, mechanical ventilation time and transfusion. For the purposes of this meta-analysis, isotonic crystalloids with supraphysiological chloride concentrations are referred to as high-chloride fluids, whereas those with near-physiological chloride concentrations are referred to as low-chloride fluids. RCTs, controlled clinical trials (CCTs) and observational studies were included in the analysis.

Studies that compared a hypertonic crystalloid with another solution were excluded from the analysis, as were studies comparing a crystalloid with a colloid, or comparing two low-chloride crystalloids. Studies were also excluded if the intravenous fluids compared were given for maintenance purposes, 'preloading/volume optimization' before surgery, priming of the cardiopulmonary bypass circuit, or the treatment of ischaemic stroke or subarachnoid haemorrhage. Study eligibility for inclusion in the meta-analysis was assessed and confirmed by two reviewers, and differences were resolved by discussion between reviewers.

Risk of bias assessment

Risk of bias was assessed using one of two approaches, depending on study design. For RCTs, the seven-category Review Manager risk of bias tool was used (RevMan version 5.2; The Cochrane Collaboration, Oxford, UK), with risk assessed as either high, unclear or low according to criteria outlined in the Cochrane Handbook for Systematic Reviews of Interventions[31]. For non-RCTs, the Newcastle–Ottawa Scale (NOS)[32] was used, in accordance with previously published methodology[33]. Briefly, the NOS allots a maximum of nine points based on the representativeness of the intervention and control groups, ascertainment of intervention, absence of outcomes at study start, comparability of groups based on study design and analysis, blinded assessment/record linkage to confirm outcomes, sufficient length of follow-up and sufficiently low withdrawal rate.

Data extraction and outcomes

Data extracted, in duplicate using a standard form, included general study characteristics (authors, design), as well as information about the study population (age, setting, condition/diagnosis), intervention (fluids compared, intervention timing and volume) and outcomes (author definition of outcome, point estimates, summary statistics, author conclusions).

For continuous variables, the mean(s.d.) value was extracted or derived from the reported data. When a study

report did not provide variability data for a point estimate, the data were requested from the study's corresponding author. Data were included in the meta-analysis only when: mean(s.d.) values could be extracted or derived from the reported data; or study authors could provide clarification. Where ventilator-free days were reported, ventilation time was derived using the period over which ventilator-free time was measured.

Statistical analysis

For dichotomous variables, RR and 95 per cent c.i. were calculated using a fixed-effect model and the Mantel–Haenszel statistical method. Studies that included a count of zero for both intervention groups for a given endpoint were not included in the analysis for that endpoint[34]. For continuous variables, the effect measure and 95 per cent c.i. were calculated using a fixed-effect model and the inverse-variance statistical method. The mean difference (MD) was used as the effect measure where all studies reported the endpoint using the same units or scale. Alternatively, the standardized mean difference (SMD), which assumes that differences in the standard deviation reflect differences in measurement scales, was used as the effect measure when different studies reported the same endpoint using different scales or units.

For continuous variables not reported as mean(s.d.) values, these statistics were derived from the reported data using published methodologies or approaches outlined in the Cochrane Handbook[31]. For continuous variables reported as median (range), the mean(s.d.) values were calculated according to methods published by Hozo and colleagues[35]. Data presented as the geometric mean (95 per cent c.i.) of log-transformed data were converted to mean(s.d.) on the raw scale using the methodology of Higgins *et al.*[36]. For further details, see *Appendix S1* (supporting information).

Forest plot generation and statistical analyses were performed using RevMan version 5.2. $P < 0{\cdot}050$ was considered to be statistically significant. The RevMan program

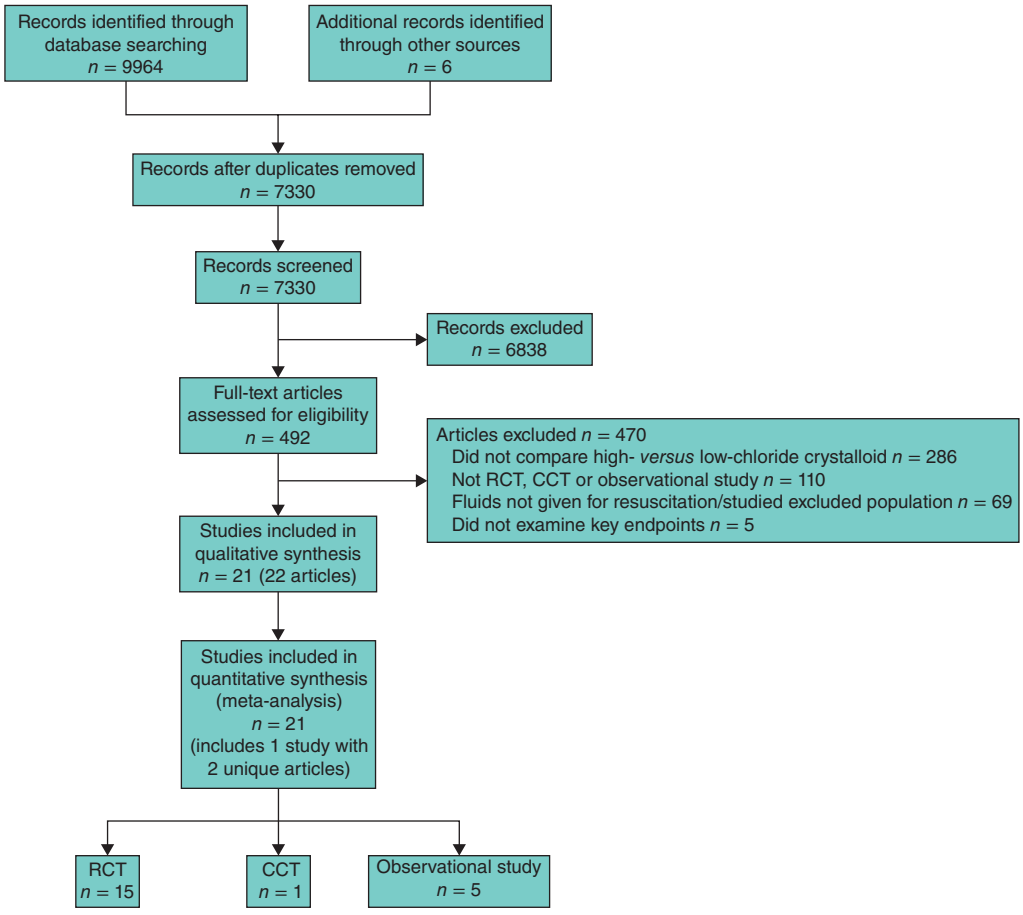

Fig. 1 PRISMA flow diagram showing study selection. RCT, randomized controlled trial; CCT, controlled clinical trial

reports *P* values to one or two significant digits; where requested, a standard normal (*Z*) table was consulted to report *P* values to three decimal places[37]. For each endpoint analysed, statistical heterogeneity was examined using the I^2 statistic, which provides an estimate of the percentage of variation across studies arising from study heterogeneity rather than chance[38]. When substantial heterogeneity (I^2 greater than 60 per cent) was detected for an endpoint showing a statistically significant effect of high- *versus* low-chloride fluids, this heterogeneity was further investigated using a random-effects analysis model or subgroup analysis, as appropriate. When visual inspection of a forest plot suggested that the overall effect was driven by a single study (weight greater than 50 per cent), sensitivity analysis excluding this study was performed[39].

Results

Included studies

In total, the database search yielded 7330 unique articles, of which 492 passed the initial screen and were reviewed for study inclusion (*Fig. 1*). Of these, 470 articles were excluded and 21 studies (in 22 articles)[10,12,14,26,27,40–56] met the inclusion criteria (*Table 1*). Studies comprised 15 RCTs and six non-RCTs, and involved 6253 patients. The study by Yunos and colleagues reported data in two unique articles, with biochemical[55] and clinical[26] outcomes published separately. Eleven studies examined critically ill patients requiring volume resuscitation in the ICU setting, and ten examined patients receiving these interventions in the perioperative period. In all included studies, the high-chloride intravenous crystalloid was 0·9 per cent saline (chloride concentration approximately 154 mmol/l) and the low-chloride intravenous crystalloid was either Ringer's lactate (chloride concentration about 109 mmol/l), Hartmann's solution (chloride concentration about 111 mmol/l) or Plasma-Lyte® (Baxter Healthcare, Deerfield, Illinois, USA) (chloride concentration 98 mmol/l). Two studies[12,40] compared three different intravenous fluids (0·9 per cent saline, Ringer's lactate and Plasma-Lyte®). For these studies, patients receiving Ringer's lactate and Plasma-Lyte® were combined into a single low-chloride fluids group by deriving pooled mean(s.d.) values from the individual group data.

Risk of bias

The overall risk of bias of RCTs meeting study inclusion criteria was acceptable (*Fig. S1*, supporting information). None of the included RCTs was judged to have a high risk of bias with respect to randomization or allocation concealment, although two studies presented unclear risks of bias, as specifics were not discussed. Blinding of participants and study personnel was ascertained for most studies; however, two reports indicated that study personnel were not blinded to the experimental intravenous fluid administered, and two additional reports did not adequately address blinding for an assessment to be made (*Table S1*, supporting information). All included non-RCTs were allotted at least six of nine possible points using the NOS, suggesting an overall acceptable risk of bias (*Fig. S2* and *Table S2*, supporting information).

Clinical endpoints

Meta-analysis results for clinical endpoints are summarized in *Figs 2–4*. No statistically significant impact on mortality was found in the six studies that included this endpoint (RR 1·13, 95 per cent c.i. 0·92, 1·39; $P = 0·230$) (*Fig. 2*). High-chloride crystalloids were associated with a significantly increased risk of AKI/renal failure (RR 1·64, 1·27 to 2·13; $P < 0·001$) (*Fig. 3*) and hyperchloraemia/metabolic acidosis (RR 2·87, 1·95 to 4·21; $P < 0·001$) (*Fig. 4*). AKI/renal failure outcomes were defined by criteria set forth by the individual studies and were not uniform. For both mortality and AKI/renal failure, heterogeneity, estimated by the I^2 statistic, was 0 per cent, suggesting a consistent direction and magnitude of effect across studies. For hyperchloraemia/metabolic acidosis, each study indicated a RR greater than 1 (range from 2·12 to 16·37), but the overall heterogeneity ($I^2 = 61$ per cent) led to a re-examination of the association using a random-effects model. This re-examination did not meaningfully change the RR (4·07, 95 per cent c.i. 1·23 to 13·53; $P = 0·022$), suggesting that the observed heterogeneity was probably due to differences in effect magnitude rather than effect direction.

Examination of ICU and/or hospital LOS revealed no significant association between chloride content and ICU LOS (SMD −0·01, 95 per cent c.i. −0·10 to 0·09; $P = 0·897$; $I^2 = 0$ per cent) (*Fig. S3*, supporting information). However, hospital LOS appeared to favour high-chloride fluids (SMD −0·07, −0·13 to −0·01; $P = 0·017$; $I^2 = 0$ per cent) (*Fig. S4*, supporting information).

Surrogate endpoints

Analysis of surrogate endpoints revealed that high-chloride intravenous fluids were associated with significantly higher serum chloride levels (MD 3·70 (95 per cent c.i. 3·36 to 4·04) mmol/l; $P < 0·001$; $I^2 = 98$ per cent) (*Fig. S5*, supporting information), greater blood transfusion volume (SMD

Table 1 Characteristics of included studies

Reference	Year	Design	Country	Study population	Total study population size	Interventions compared	Key endpoints
Berger *et al.*[41]	2000	Retrospective	Switzerland	Adults with thermal burns	40	Bicarbonated 0·9% saline *versus* Ringer's lactate	Mortality, acute renal injury, ICU LOS, mechanical ventilation time, hyperchloraemia/metabolic acidosis, urine output
Cho *et al.*[42]	2007	RCT	Korea	Adults with rhabdomyolysis	28	0·9% saline *versus* Ringer's lactate	Serum chloride
Chua *et al.*[43]	2012	Retrospective	Australia	Adults with severe DKA	23	0·9% saline *versus* Plasma-Lyte® 148	ICU LOS, urine output
Cieza *et al.*[44]	2013	Observational	Peru	Adults with severe dehydration	40	0·9% saline *versus* Ringer's lactate	Serum creatinine, serum chloride
Hadimioglu *et al.*[12]	2008	RCT	Turkey	Adults undergoing kidney transplantation	90*	0·9% saline *versus* Plasma-Lyte® and Ringer's lactate	Acute renal injury, serum creatinine, serum chloride, urine output
Hasman *et al.*[40]	2012	RCT	Turkey	Adults with moderate or severe dehydration	90*	0·9% saline *versus* Plasma-Lyte® and Ringer's lactate	Serum chloride
Khajavi *et al.*[45]	2008	RCT	Iran	Adults undergoing kidney transplantation	52	0·9% saline *versus* Ringer's lactate	Serum creatinine, urine output
Kim *et al.*[46]	2013	RCT	Korea	Adults undergoing kidney transplantation	60	0·9% saline *versus* Plasma-Lyte® A	Serum creatinine, serum chloride, urine output, transfusion volume
Mahajan *et al.*[47]	2012	RCT	India	Children with severe dehydration	22	0·9% saline *versus* Ringer's lactate	Mortality, hospital LOS, serum chloride
Mahler *et al.*[48]	2011	RCT	USA	Adults with DKA	45	0·9% saline *versus* Plasma-Lyte® A	Serum chloride
Modi *et al.*[49]	2012	RCT	Saudi Arabia	Adults undergoing kidney transplantation	74	0·9% saline *versus* Ringer's lactate	Serum chloride, serum creatinine
O'Malley *et al.*[50]	2005	RCT	USA	Adults undergoing renal transplantation	51	0·9% saline *versus* Ringer's lactate	Acute renal injury, hospital LOS, hyperchloraemia/metabolic acidosis, serum creatinine, serum chloride, urine output
Scheingraber *et al.*[10]	1999	RCT	Germany	Adults undergoing elective abdominal gynaecological surgery	24	0·9% saline *versus* Ringer's lactate	Urine output
Shaw *et al.*[27]	2012	Retrospective	USA	Adult surgical patients	3704†	0·9% saline *versus* Plasma-Lyte® 148 or Plasma-Lyte® A	Mortality, acute kidney injury, hospital LOS, mechanical ventilation time
Takil *et al.*[51]	2002	RCT	Turkey	Adult spinal surgery patients	30	0·9% saline *versus* Ringer's lactate	Hospital LOS, ICU LOS, serum chloride, urine output, transfusion volume
Van Zyl *et al.*[52]	2012	RCT	South Africa	Adults with DKA	54	0·9% saline *versus* Ringer's lactate	Hospital LOS, serum creatinine, serum chloride
Waters *et al.*[14]	2001	RCT	USA	Adult patients undergoing aortic reconstructive surgery	66	0·9% saline *versus* Ringer's lactate	Mortality, acute renal injury, hospital LOS, ICU LOS, mechanical ventilation time, serum creatinine, serum chloride, urine output, transfusion volume
Wu *et al.*[53]	2011	RCT	USA	Adults with acute pancreatitis	40	0·9% saline *versus* Ringer's lactate	Acute renal injury, hospital LOS
Young *et al.*[54]	2014	RCT	USA	Adults with traumatic injury	65	0·9% saline *versus* Plasma-Lyte® A	Mortality, acute renal injury, hospital LOS, ICU LOS, mechanical ventilation time, serum creatinine, serum chloride, urine output, transfusion volume
Yunos *et al.*[26,55]	2011, 2012	CCT	Australia	Adult ICU patients	1533	Chloride-rich fluids (0·9% saline, 4% succinylated gelatin solution, 4% albumin) *versus* balanced solutions (Hartmann's, Plasma-Lyte® 148, chloride-poor 20% albumin)	Mortality, acute renal injury, hospital LOS, ICU LOS, serum chloride, serum creatinine, urine output
Zunini *et al.*[56]	2011	Retrospective	Uruguay	Children undergoing craniofacial surgery	122	0·9% saline *versus* Ringer's lactate	Hyperchloraemia/metabolic acidosis

*Studies compared three different intravenous fluids: 0·9 per cent saline, Ringer's lactate and Plasma-Lyte® (Baxter Healthcare, Deerfield, Illinois, USA); pooled means and variances were derived for the Ringer's lactate and Plasma-Lyte® groups in both cases. †Propensity-matched population. ICU, intensive care unit; LOS, length of stay; RCT, randomized controlled trial; DKA, diabetic ketoacidosis; CCT, controlled clinical trial.

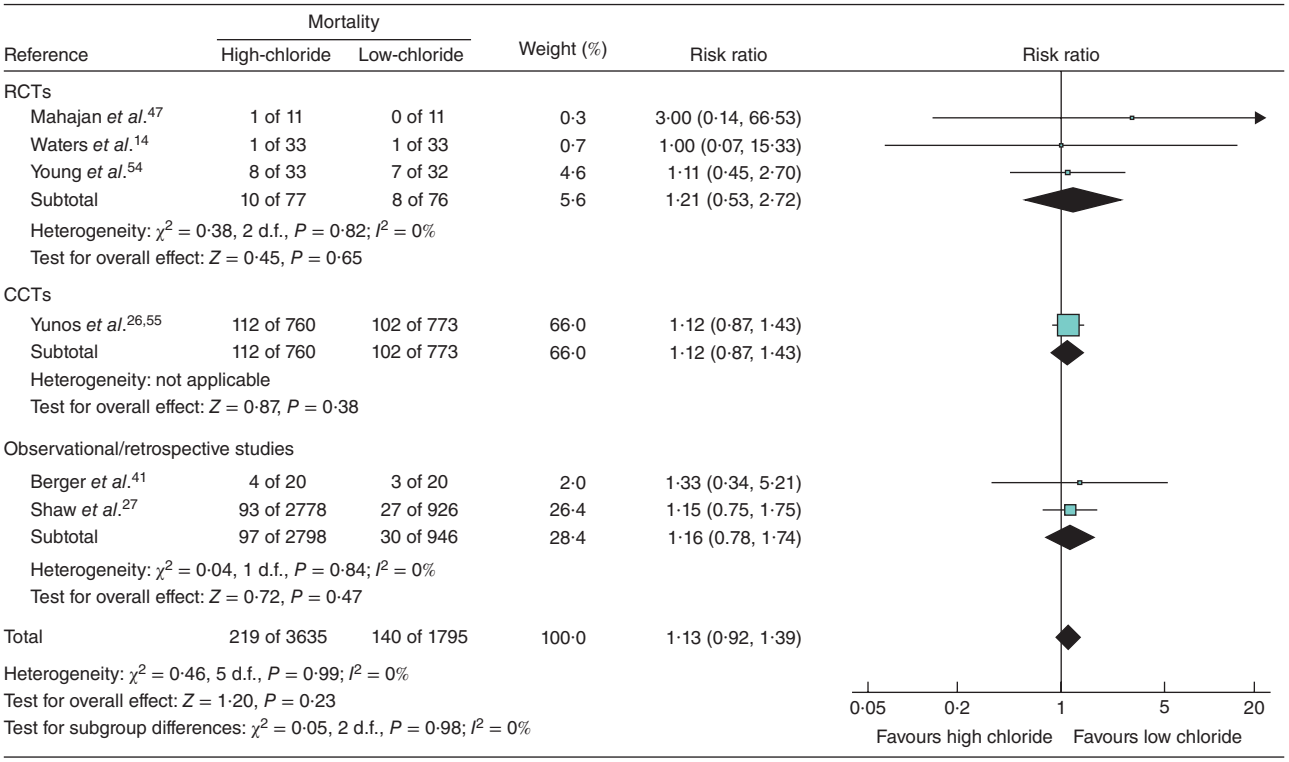

Fig. 2 Forest plot illustrating mortality risk following volume resuscitation with high-chloride *versus* low-chloride intravenous fluids. Where necessary, mortality incidence was derived from reported survival. A Mantel–Haenszel fixed-effect model was used for meta-analysis. Risk ratios are shown with 95 per cent c.i. RCT, randomized controlled trial; CCT, controlled clinical trial

0·35, 0·07 to 0·63; $P = 0·014$; $I^2 = 0$ per cent) (*Fig. 5*) and longer mechanical ventilation time (SMD 0·15, 0·08 to 0·23; $P < 0·001$; $I^2 = 17$ per cent) (*Fig. S6*, supporting information). There was no significant difference between high- *versus* low-chloride intravenous fluids with respect to serum creatinine levels (SMD 0·10, −0·02 to 0·23; $P = 0·095$; $I^2 = 18$ per cent) (*Fig. S7*, supporting information) and a small effect on urine output (SMD 0·17, 0·02 to 0·32; $P = 0·030$; $I^2 = 70$ per cent) (*Fig. S8*, supporting information). Given the observed heterogeneity, urine output was re-evaluated using a random-effects model, which demonstrated a non-significant effect of high- *versus* low-chloride intravenous fluids (SMD 0·08, −0·22 to 0·38; $P = 0·589$).

Sensitivity analyses

For some endpoints, forest plot inspection indicated that overall effect measures were driven largely by a single heavily weighted study (in all cases, either Yunos *et al.*[26,55], Zunini *et al.*[56] or Shaw *et al.*[27]). To understand how these individual studies might influence effect estimates, sensitivity analyses were repeated after excluding them. Exclusion of the Yunos *et al.*[26,55] and Zunini *et al.*[56] studies from the analyses of AKI/renal failure, hyperchloraemia/metabolic acidosis and serum chloride did not affect the direction of effect, but did convert to a non-statistically significant effect for the AKI/renal failure endpoint (*Table 2*). Exclusion of the Shaw *et al.*[27] study from the pooled analysis of mechanical ventilation time also resulted in a shift to an effect that was not statistically significant. Similarly, when the Shaw *et al.*[27] study was excluded from the LOS analyses, no statistically significant effect was observed. Exclusion of the Yunos *et al.*[26] study from the mortality analysis had no impact.

Significant heterogeneity with respect to reported serum chloride levels ($I^2 = 98$ per cent) was investigated by subgroup analysis based on timing of chloride measurement and by using a random-effects model. Although high-chloride fluids were associated with higher serum chloride levels in both RCT subgroups (*Fig. S5*, supporting information), this analysis suggests that subgroup differences do exist based on time point of measurement (MD 11·18 (95 per cent c.i. 10·29 to 12·06) mmol/l; $P < 0·001$ for studies reporting intraoperative or postoperative levels, *versus* MD 2·24 (1·60 to 2·89) mmol/l; $P < 0·001$ for studies reporting levels at other time points). Analysis of

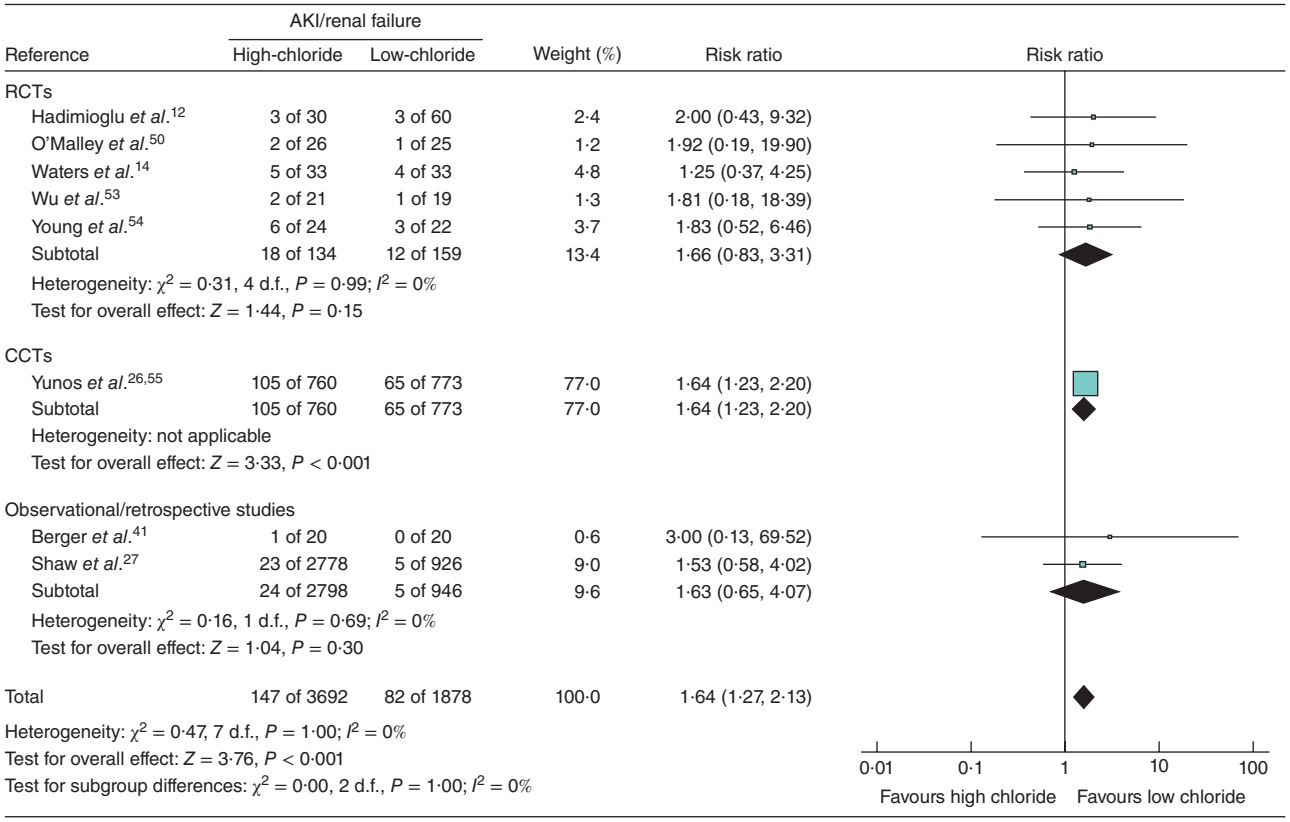

Fig. 3 Forest plot illustrating acute kidney injury (AKI)/renal failure risk following volume resuscitation with high-chloride *versus* low-chloride intravenous fluids. A Mantel–Haenszel fixed-effect model was used for meta-analysis. Risk ratios are shown with 95 per cent c.i. RCT, randomized controlled trial; CCT, controlled clinical trial

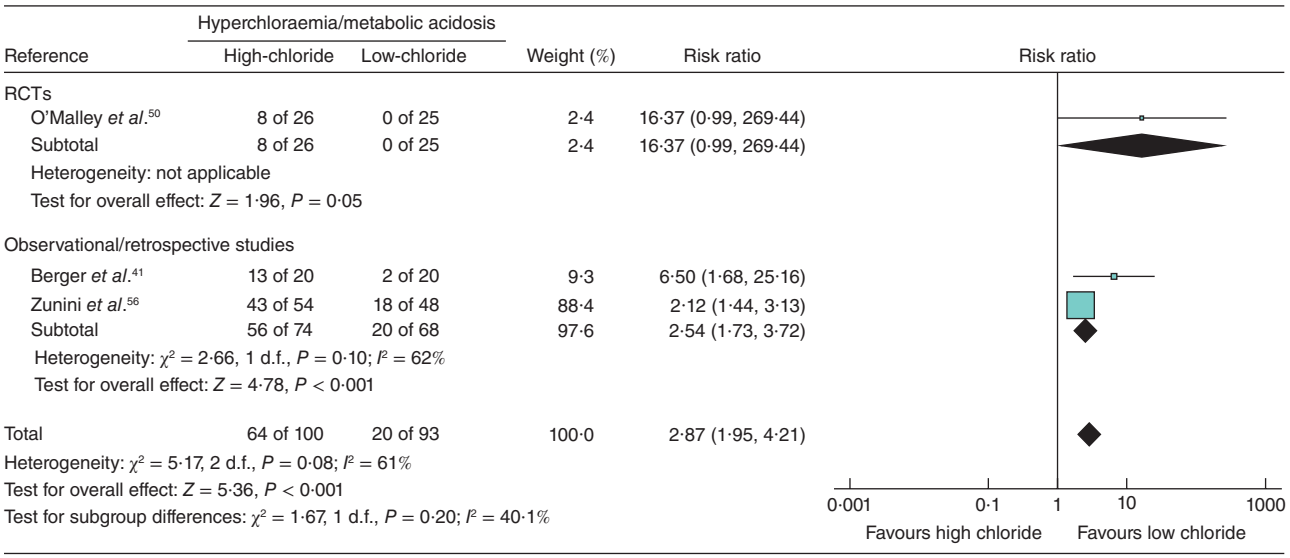

Fig. 4 Forest plot illustrating hyperchloraemia/metabolic acidosis risk following volume resuscitation with high-chloride *versus* low-chloride intravenous fluids. A Mantel–Haenszel fixed-effect model was used for meta-analysis. Risk ratios are shown with 95 per cent c.i. RCT, randomized controlled trial; CCT, controlled clinical trial

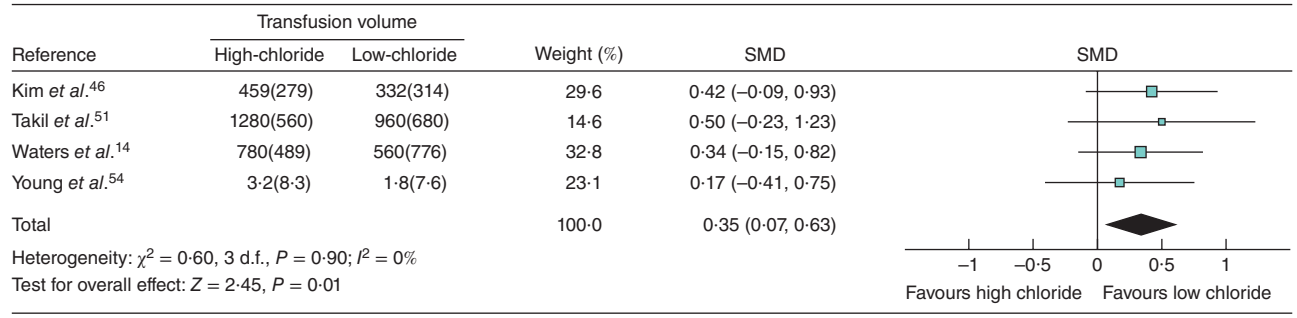

Fig. 5 Forest plot illustrating mean(s.d.) blood transfusion volume following volume resuscitation with high-chloride *versus* low-chloride intravenous fluids. All included studies reporting this endpoint were randomized controlled trials. An inverse-variance fixed-effect model was used for meta-analysis. Standardized mean differences (SMDs) are shown with 95 per cent c.i.

Table 2 Summary of sensitivity analyses

	Overall analysis		Sensitivity analysis			
			Excluded study			
	Effect size	*P*	Reference	Weight (%)	Effect size	*P*
Clinical endpoints						
Acute kidney injury	RR 1·64 (1·27, 2·13)	< 0·001	Yunos *et al.*[26]	77·0	RR 1·65 (0·95, 2·87)	0·078
Hyperchloraemia/metabolic acidosis	RR 2·87 (1·95, 4·21)	< 0·001	Zunini *et al.*[56]	65·5	RR 8·50 (2·49, 29·08)	0·001
Mortality	RR 1·13 (0·92, 1·39)	0·230	Yunos *et al.*[26]	65·0	RR 1·17 (0·81, 1·68)	0·401
ICU LOS	SMD –0·01 (–0·10, 0·09)	0·897	Yunos *et al.*[26]	88·7	SMD –0·07 (–0·35, 0·21)	0·624
Hospital LOS	SMD –0·07 (–0·13, –0·01)	0·017	Shaw *et al.*[27]	60·1	SMD –0·01 (–0·10, 0·08)	0·849
Surrogate endpoints						
Serum chloride	MD 3·70 (3·36, 4·04)	< 0·001	Yunos *et al.*[55]	55·3	MD 5·31 (4·79, 5·82)	< 0·001
Mechanical ventilation time	SMD 0·15 (0·08, 0·23)	< 0·001	Shaw *et al.*[27]	95·1	SMD –0·06 (–0·38, 0·27)	0·734

Values in parentheses are 95 per cent c.i. RR, risk ratio; ICU, intensive care unit; LOS, length of stay; SMD, standardized mean difference; MD, mean difference.

serum chloride using a random-effects model revealed no significant change in effect measure or significance (MD 5·06 (2·30 to 7·82) mmol/l; $P < 0·001$).

Two studies[47,56] included in the present analysis involved paediatric patients. Although both studies were small (22 and 122 patients respectively) and therefore unlikely to impact significantly on the effect estimates, sensitivity analysis excluding these two trials was performed in order to account for potential differences in fluid physiology in paediatric *versus* adult patients. There was no impact on either effect direction or significance for any of the measured endpoints when these studies were excluded: mortality (RR 1·13, 95 per cent c.i. 0·92 to 1·39; $P = 0·250$), hospital LOS (SMD −0·07, −0·13 to −0·02; $P = 0·013$), hyperchloraemia/metabolic acidosis (RR 8·50, 2·49 to 29·0; $P < 0·001$) or serum chloride (MD 4·02 (3·66 to 4·37) mmol/l; $P < 0·001$).

Discussion

Meta-analysis of all available studies demonstrated a significantly higher risk of AKI, metabolic acidosis, blood transfusion and time on mechanical ventilation with high-chloride fluid resuscitation. The association between high-chloride fluids, metabolic acidosis and higher serum chloride levels is supported by several studies[10,11,54] that did not meet the inclusion criteria for the present meta-analysis, and provides face validity for a conceptual mechanism of deleterious effects of hyperchloraemia. No increased risk for mortality was found.

High-chloride fluids were significantly associated with an increased risk of AKI/renal failure. This endpoint was driven heavily by one study[26], and sensitivity analysis excluding this study showed the same direction of effect, but loss of statistical significance. Each remaining study demonstrated a directionally similar association between increased AKI/renal failure and high-chloride fluids. One limitation in interpreting these data is the lack of uniformity among definitions of AKI. Ideally a standardized definition would be applied for the analysis; however, this was not possible with the available data. Moreover, serum creatinine concentration, a surrogate marker of renal function, did not demonstrate an association with the fluid chloride content. Failure to detect such an association

may be related to reporting of serum creatinine levels at variable time points, and the possibility that the magnitude of differences in serum creatinine concentration may vary with time.

Greater urine output was significantly associated with high-chloride fluids, which may appear inconsistent with greater risk of AKI. However, the effect of fluid chloride content on urinary output may be largely time-dependent[57,58], and in this context urine output may not be a useful surrogate measure of renal function. Variability in the timing of urine output measurements and diuretic use may also confound these results. In light of the variability in AKI/renal failure definitions, timing of creatinine measurement and effects on urine output, this AKI harm signal should be interpreted cautiously.

No reported difference in mortality may reflect either no true difference, variability in the time periods over which mortality was reported, inadequate sample size to detect a difference, or variability in the risk factors in the included patient populations. Because this meta-analysis included studies in both perioperative and ICU settings, lower-risk patients were included than if the analysis had been limited solely to critical illness, lowering the overall mortality rate and thus decreasing the likelihood of detecting a possible mortality signal. It is also conceivable that an increased risk of AKI may occur without an increase in short-term mortality. These factors may help to explain why an increase in AKI, but not mortality, was observed with high-chloride crystalloid use in this meta-analysis.

Two recent studies ineligible for this meta-analysis have examined the relationship between mortality and either hyperchloraemia[25] or crystalloid fluid choice[59]. A retrospective, propensity-matched, cohort study[25] of surgical patients demonstrated a significant association between hyperchloraemia and mortality, as well as AKI. Notably, the relationship between serum chloride and fluid administered was not assessed. In a propensity-matched cohort study[59] of non-operative patients with vasopressor-dependent sepsis, use of balanced fluids (low-chloride by the present definition) was associated with lower in-hospital mortality, but no effect was found for AKI. One could infer that, because high-chloride fluids lead to hyperchloraemia and hyperchloraemia is associated with mortality, high-chloride fluids must be associated with mortality. However, the relationship is not clearly true in all populations studied and may vary based on risk.

Among the four eligible studies[14,46,51,54] reporting transfusion outcomes, all reported at least a small or modest[31,60] increase in transfusion volume with high-chloride fluid administration. Shaw and co-workers[27] also demonstrated an association between high-chloride fluids and greater transfusion volume, but the study was not included in the analysis owing to lack of variability data. Although the total number of patients included in the present meta-analysis of blood transfusion volume was low (high-chloride, 102; low-chloride, 100), the potential for a true difference raises relevant questions. Clinicians may consider any difference meaningful given the expense and risks associated with red cell transfusions[61,62]. Although causality has not been established between high-chloride fluids and increased transfusion, the potential clinical impact of a true effect is hypothesis-generating.

When administered in large volumes, 0·9 per cent saline has been shown to cause coagulopathy[63,64]. Total volumes of fluid administered did not vary substantially between the groups (*Table S3*, supporting information), suggesting that dilutional coagulopathy does not account for the observed differences in transfusion. Mechanisms of saline-induced coagulopathy are not fully known, and the data lead us to consider whether hyperchloraemia/acidosis has an independent effect on coagulation. Alternatively, a reverse association cannot be excluded, in that fewer transfusions may have been administered in the low-chloride groups owing to the possibility of incompatibility with citrated blood. However, in two[46,54] of the four studies, the low-chloride solution did not contain calcium, and in one[14] of the other studies the providers were blinded to the fluid that was being administered.

Findings for additional endpoints investigated should not be considered definitive, owing to the low event rate and small sample size. Further studies including these endpoints are needed to arrive at firm conclusions.

Combining RCTs, CCTs and observational studies may provide more generalizable results and help to offset the limitations that accompany the often low event rates in smaller RCTs[33,65–68]. In addition, a recent meta-analysis[68] demonstrated no significant differences between the risks of adverse events between RCTs and observational studies, leading the authors to advocate the inclusion of a broad range of studies when analysing harm signals. The present authors believe that the addition of observational data strengthens this study and the influence of observable confounding variables is specifically reduced by propensity-matching.

Combining RCTs and non-RCTs could alternatively be viewed as a limitation of this study, as some advocate that data from RCTs and observational studies should not be pooled for analysis; rather, if the RCTs and observational studies warrant equal confidence, both types of evidence should be presented separately[69]. As such, in addition to presenting the overall effect in the forest plots, the studies are grouped by type so that plots may be visualized

accordingly. Despite inclusion of observational studies, the total number of patients remains low and several outcomes were examined in only a small number of studies. Further limitations include variability in the populations studied, the potential for significant bias in observational studies, and variability in outcome assessment. There is also potential for bias due to the exclusion of abstracts and non-English-language manuscripts. Assessment for publication bias was not possible owing to the small number of studies that met the inclusion criteria.

The present findings argue against the intravenous administration of supraphysiological concentrations of chloride (above 111 mmol/l), yet most studies were small in size, thereby preventing firm conclusions from being drawn. These findings underscore the need for large, well designed RCTs that are adequately powered to detect differences in outcomes such as mortality and morbidity, including AKI. This provides an opportunity for international collaboration[70] in surgical and critical care research; already, the Australian and New Zealand Intensive Care Society (ANZICS) Clinical Trials Group has begun enrolment in the SPLIT study[71] comparing 0·9 per cent saline with Plasma-Lyte® 148 for fluid therapy in the ICU. Future considerations could include *a priori* subgroup distinctions such as comparison of medical *versus* surgical patients, or low-risk *versus* high-risk surgical patients.

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Supporting information

Additional supporting information may be found in the online version of this article:

Appendix S1 Electronic health database search terms (Word document)

Fig. S1 Risk of bias graph for randomized controlled trials meeting meta-analysis inclusion criteria (Word document)

Fig. S2 Risk of bias graph for non-randomized studies meeting meta-analysis inclusion criteria (Word document)

Fig. S3 Analysis of intensive care unit (ICU) length of stay following volume resuscitation with high-chloride *versus* low-chloride intravenous fluids (Word document)

Fig. S4 Analysis of hospital length of stay following volume resuscitation with high-chloride *versus* low-chloride intravenous fluids (Word document)

Fig. S5 Serum chloride concentration following volume resuscitation with high-chloride *versus* low-chloride intravenous fluids (Word document)

Fig. S6 Analysis of mechanical ventilation time following volume resuscitation with high-chloride *versus* low-chloride intravenous fluids (Word document)

Fig. S7 Analysis of serum creatinine concentration following volume resuscitation with high-chloride *versus* low-chloride intravenous fluids (Word document)

Fig. S8 Analysis of urine output following volume resuscitation with high-chloride *versus* low-chloride intravenous fluids (Word document)

Table S1 Risk of bias of included randomized controlled trials (Word document)

Table S2 Risk of bias of included non-randomized studies (Word document)

Table S3 Study fluid volumes received (Word document)