Systematic review

Meta-analysis of colloids *versus* crystalloids in critically ill, trauma and surgical patients

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Background: **There is uncertainty regarding the safety of different volume replacement solutions. The aim of this study was systematically to review evidence of crystalloid *versus* colloid solutions, and to determine whether these results are influenced by trial design or clinical setting.**

Methods: **PubMed, Embase and the Cochrane Central Register of Controlled Trials were used to identify randomized clinical trials (RCTs) that compared crystalloids with colloids as volume replacement solutions in patients with traumatic injuries, those undergoing surgery and in critically ill patients. Adjusted odds ratios (ORs) for mortality and major morbidity including renal injury were pooled using fixed-effect and random-effects models.**

Results: **Some 59 RCTs involving 16 889 patients were included in the analysis. Forty-one studies (69 per cent) were found to have selection, detection or performance bias. Colloid administration did not lead to increased mortality (32 trials, 16 647 patients; OR 0·99, 95 per cent c.i. 0·92 to 1·06), but did increase the risk of developing acute kidney injury requiring renal replacement therapy (9 trials, 11 648 patients; OR 1·35, 1·17 to 1·57). Sensitivity analyses that excluded small and low-quality studies did not substantially alter these results. Subgroup analyses by type of colloid showed that increased mortality and renal replacement therapy were associated with use of pentastarch, and increased risk of renal injury and renal replacement therapy with use of tetrastarch. Subgroup analysis indicated that the risks of mortality and renal injury attributable to colloids were observed only in critically ill patients with sepsis.**

Conclusion: **Current general restrictions on the use of colloid solutions are not supported by evidence.**

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Introduction

Uncertainty about the appropriate choice of fluid for volume replacement persists. The recent CHEST (crystalloid *versus* hydroxyethyl starch) trial[1] and Scandinavian 6S (Starch for Severe Sepsis/Septic Shock) trial[2] demonstrated increased risks of death and acute kidney injury in patients receiving modern hydroxyethyl starch (HES) (tetrastarch 130/0·4). Conversely, the FIRST (Fluids in Resuscitation of Severe Trauma)[3], BaSES (Basel Starch Evaluation in Sepsis)[4] and CRISTAL (Colloids *versus* Crystalloids for the Resuscitation of the Critically Ill)[5] trials did not demonstrate increased harm with HES administration compared with crystalloid. Comparison of these trials is limited by different indications for volume replacement and total volumes of colloids administered. The choice of crystalloid used as a control differs between the studies, adding further complexity as analyses suggest that the use of balanced salt solutions may result in better clinical outcomes than use of 0·9 per cent saline[6,7]. Despite this uncertainty, evidence of harm attributable to HES solutions in some trials has resulted in regulatory steps to suspend marketing authorization of these colloids[8]. This increases the likelihood that patients will be exposed to larger volumes of crystalloid, which may also have unrecognized adverse effects[9].

To analyse the interaction between choice of volume replacement solution and the clinical context in which these solutions are used, a systematic review and meta-analysis was undertaken of randomized clinical trials (RCTs) that compared colloid with crystalloid solutions for volume replacement in sepsis, critical care, during and after major surgery, and trauma. Outcomes of interest were mortality, acute kidney injury, acute renal failure,

renal replacement therapy, duration of intensive care unit (ICU) stay and length of hospital stay.

Methods

A prespecified protocol was developed and followed, which detailed the objectives, criteria for study selection, the approach to assessing risk of bias, clinical outcomes, and statistical methodology. The study adhered to the Preferring Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.

Study identification

Published RCTs comparing any non-blood fluid therapy (tetrastarch – balanced and unbalanced, pentastarch, hexastarch, hetastarch, dextrans, gelatins, hypertonic solutions, Ringer's lactate and normal saline) in adult patients undergoing major surgery (vascular, cardiac, abdominal and orthopaedic surgery), patients who had sustained major trauma, or patients who had been admitted to critical care with sepsis or septic shock, were identified.

For injured patients, prehospital and postadmission RCTs were included. For patients undergoing non-trauma surgery, RCTs reporting on perioperative (induction or maintenance) and postoperative use of colloid *versus* crystalloid solutions were included in the study. In patients undergoing cardiac surgery, RCTs reporting on the use of fluid therapy as a pump prime along with perioperative maintenance and postoperative resuscitation were included.

The primary outcomes were risk of mortality, acute kidney injury and need for renal replacement therapy. The secondary outcomes were risk of sepsis, myocardial infarction, stroke, and duration of ICU and hospital stay.

Non-RCT studies, reviews, paediatric and transplant populations were excluded. Trials comparing albumin in single head-to-head analyses were also excluded as these have been reviewed recently[10].

Search strategy

A search was undertaken using electronic databases (MEDLINE, Embase, Cochrane Central Register of Controlled Trials and Database of Abstracts of Reviews of Effects (DARE)) from inception to 2014 using prespecified key words (*Appendix S1*, supporting information). Reference lists and bibliographical data of pertinent RCTs and systematic reviews were hand-searched for additional relevant articles.

Data collection

Data on demographics, methods, results and bias were collected by two independent reviewers. Any disagreement was resolved by discussion. Selected authors of publications were contacted individually for clarification of eligibility and analysis (those reporting per-protocol analyses and interquartile range, and studies with missing data).

Assessment of methodological quality

Using Grading of Recommendations Assessment, Development and Evaluation (GRADE) methodology, risk of bias was used to guide whether trials had limitations. Limitation was defined as presence of poor design or its implementation, indirectness of evidence (indirect population, intervention, control, outcome), unexplained heterogeneity or inconsistency of results, imprecision of results or high probability of publication bias. GRADE Pro-software, version 3.2 for Windows® (J. Brozek, A. Oxman, H. Schünemann, 2008) was used to undertake GRADE quality assessment of outcomes.

Data extraction

Data were extracted by two reviewers using a specifically designed pro forma. This incorporated assessment of trial design, demographics, details of interventions, details of outcomes and author judgement of risk of bias. Additional data regarding type of analysis (per protocol and intention to treat) and follow-up were also recorded. Information was also obtained on the method of definition of acute kidney injury or acute renal failure, such as use of the Risk, Injury, Failure, Loss of kidney Function and End-stage Kidney disease (RIFLE) or Acute Kidney Injury Network (AKIN) classifications. Standard errors of the mean and interquartile ranges were converted to standard deviations using appropriate formulas.

Data analysis

Dichotomous outcomes (mortality, sepsis, stroke, myocardial infarction, need for renal replacement therapy and incidence of acute kidney injury or acute renal failure) are presented as odds ratios (ORs) with 95 per cent c.i., calculated using a fixed-effect model. A random-effects model using Mantel–Haenszel method was also used to analyse these outcomes. Several trials reported zero events for certain outcomes in both treatment and control groups. These trials were included in the present analyses as their exclusion could inflate the size of pooled treatment effects[11]. Continuous outcomes (duration of ICU and hospital stay)

were pooled as weighted mean differences (MDs). Heterogeneity was assessed with I^2 statistics; an I^2 value greater than or equal to 50 per cent was considered to indicate substantial heterogeneity in this analysis. Meta-analysis was performed in line with the Cochrane Collaboration and the quality of reporting of meta-analyses guidelines[12]. Publication bias was evaluated by inspection of funnel plots.

Subgroup and sensitivity analyses

Sources of heterogeneity were explored by conducting subgroup analyses by type of colloid (tetrastarch, pentastarch, dextrans and gelatin) and clinical settings (trauma, sepsis, general and cardiac surgery). Sensitivity analyses were conducted by exclusion of low-volume studies (fewer than 250 patients) and after exclusion of low-quality studies (those with limitations based on GRADE). An additional sensitivity analysis in the colloid *versus* colloid comparison was also undertaken by excluding certain studies owing to reporting of fabricated results[13,14] and lack of institutional ethical approval[15]. None of these studies was included in the colloid *versus* crystalloid analyses.

All analyses were carried out using Review Manager (RevMan) version 5.1 (The Nordic Cochrane Centre, Copenhagen, Denmark).

Results

Characteristics of studies

A PRISMA flow diagram showing overall search strategy is shown in *Fig. 1*. A total of 59 RCTs[1–4,7,13,14,16–67] comparing non-blood fluid therapies were included in the meta-analyses. Characteristics of these studies are shown in *Table S1* (supporting information). Twenty-one (36 per cent) of the included studies were in cardiac surgery, 13 (22 per cent) in critical care or sepsis, 12 (20 per cent) in trauma, six (10 per cent) in abdominal or general surgery, two (3 per cent) in aortic surgery, two (3 per cent) in orthopaedic surgery, one (2 per cent) in urological surgery, one (2 per cent) concerned heart failure and one (2 per cent) pancreatitis.

Of the studies reporting outcomes in cardiac surgery, all used cardiopulmonary bypass, except for two studies[41,56] that employed the off-pump technique. Of the 21 studies, seven evaluated the study fluid as pump prime, and the remaining 14 evaluated perioperative volume replacement solutions. In patients with sepsis (13 studies), one trial[22] analysed mechanically ventilated patients with respiratory failure, whereas another[62] examined patients with hypoalbuminaemia in the ICU. The remaining 11 trials considered patients with severe sepsis or septic shock.

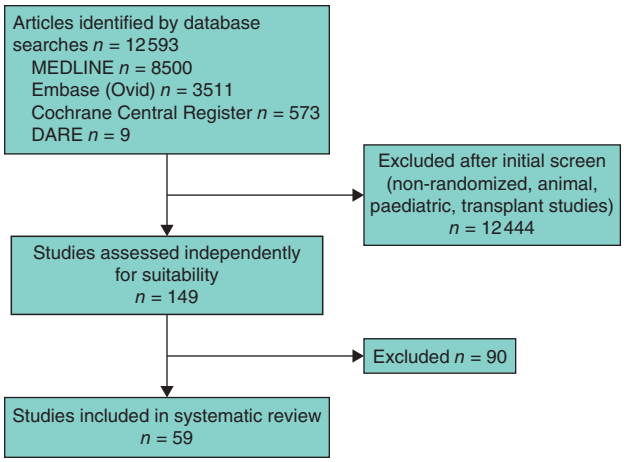

Fig. 1 PRISMA diagram showing selection of articles for review. DARE, Database of Abstracts of Reviews of Effects

Tetrastarch (130/0·42) was compared in 25 (42 per cent) of the included studies, pentastarch (200/0·5, 250/0·45, 70/0·45) in 11 (19 per cent), hexastarch (200/0·62) in two (3 per cent), hetastarch (450/0·7) in two (3 per cent), hypertonic saline (7·5 per cent)–dextran in 13 (22 per cent), dextran alone (dextran-70) in one (2 per cent), gelatin in 15 (25 per cent), lactated Ringer's in 19 (32 per cent) studies and normal saline in 22 (37 per cent). There was considerable variation in the doses of pentastarch (28–70 ml/kg) and tetrastarch (27–50 ml/kg) administered.

Mortality was reported by 53 studies (90 per cent). Acute renal failure or acute kidney injury was reported in 21 studies (36 per cent), need for renal replacement therapy in 13 (22 per cent), myocardial infarction in nine (15 per cent), sepsis in seven (12 per cent), stroke in eight (14 per cent) and length of stay in 24 (41 per cent). Of the RCTs reporting acute renal failure or acute kidney injury, six did not define the method of outcome assessment, four used the RIFLE method alone, one used a combination of AKIN and RIFLE criteria, six employed only a creatinine-based method, and the remainder used a combination of reduction in glomerular filtration rate, increase in serum creatinine level and need for renal replacement therapy as qualifying criteria.

Risk of bias

Inter-rater agreement for both eligibility and quality of methodology was good ($\kappa = 0{\cdot}74$). Random sequence generation was reported by 31 RCTs (53 per cent), concealment of allocation by 32 (54 per cent), blinding of participants by 31 (53 per cent), blinding of outcome assessment by nine (15 per cent), incomplete outcome

Reference	Mortality		Weight (%)	Odds ratio
	Colloids	Crystalloids		
Tetrastarch				
Alavi *et al.*[16]	0 of 32	0 of 29		Not estimable
Annane *et al.*[20]	362 of 1290	372 of 1107	18·5	0·77 (0·65, 0·92)
Dubin *et al.*[28]	1 of 9	5 of 11	0·2	0·21 (0·03, 1·38)
Guidet *et al.*[33]	31 of 100	24 of 95	1·4	1·33 (0·71, 2·47)
Gurbuz *et al.*[34]	0 of 100	0 of 100		Not estimable
Haase *et al.*[4]	44 of 117	50 of 124	2·1	0·89 (0·53, 1·50)
Hamaji *et al.*[35]	1 of 24	0 of 24	0·0	7·39 (0·15, 372·38)
Harten *et al.*[36]	1 of 14	2 of 15	0·1	0·52 (0·05, 5·50)
Hung *et al.*[37]	0 of 41	0 of 39		Not estimable
James *et al.*[3]	12 of 56	6 of 53	0·6	2·07 (0·76, 5·66)
Myburgh *et al.*[1]	597 of 3315	566 of 3336	35·1	1·07 (0·95, 1·22)
Perner *et al.*[2]	201 of 398	172 of 400	7·3	1·35 (1·02, 1·78)
Yates *et al.*[65]	5 of 104	2 of 98	0·2	2·28 (0·51, 10·26)
Subtotal	1255 of 5600	1199 of 5431	65·5	1·01 (0·92, 1·10)
Heterogeneity: $\chi^2 = 22{\cdot}40$, 9 d.f., $P = 0{\cdot}008$; $I^2 = 60\%$				
Test for overall effect: $Z = 0{\cdot}14$, $P = 0{\cdot}89$				
Pentastarch				
Brunkhorst *et al.*[24]	107 of 261	93 of 274	4·6	1·35 (0·95, 1·92)
Magder *et al.*[42]	2 of 119	2 of 118	0·1	0·99 (0·14, 7·13)
McIntyre *et al.*[46]	9 of 21	6 of 19	0·4	1·60 (0·45, 5·67)
Veneman *et al.*[62]*	9 of 15	5 of 16	0·3	3·08 (0·76, 12·38)
Veneman *et al.*[62]†	9 of 15	5 of 16	0·3	3·08 (0·76, 12·38)
Subtotal	136 of 431	111 of 443	5·7	1·47 (1·08, 2·02)
Heterogeneity: $\chi^2 = 2{\cdot}55$, 4 d.f., $P = 0{\cdot}64$; $I^2 = 0\%$				
Test for overall effect: $Z = 2{\cdot}41$, $P = 0{\cdot}02$				
Hypertonic saline–dextran				
Alpar and Killampalli[18]	7 of 90	12 of 90	0·6	0·56 (0·22, 1·44)
Bueno *et al.*[25]	0 of 25	0 of 25		Not estimable
Bulger *et al.*[26]	32 of 110	22 of 99	1·5	1·43 (0·77, 2·65)
Bulger *et al.*[27]‡	53 of 220	66 of 256	3·2	0·91 (0·60, 1·39)
Bulger *et al.*[27]§	53 of 220	94 of 376	3·8	0·95 (0·65, 1·40)
Mattox *et al.*[44]	35 of 184	42 of 175	2·2	0·74 (0·45, 1·23)
Morrison *et al.*[47]	35 of 50	42 of 57	0·8	0·83 (0·36, 1·94)
Oliveira *et al.*[48]	4 of 13	10 of 16	0·3	0·29 (0·07, 1·24)
Rizoli *et al.*[52]	0 of 10	2 of 14	0·1	0·17 (0·01, 2·95)
Vassar *et al.*[61]¶	27 of 49	23 of 45	0·9	1·17 (0·52, 2·63)
Vassar *et al.*[61]#	22 of 50	23 of 45	0·9	0·75 (0·34, 1·68)
Younes *et al.*[66]	0 of 35	1 of 35	0·0	0·14 (0·00, 6·82)
Younes and Birolini[67]	27 of 101	40 of 111	1·7	0·65 (0·37, 1·16)
Subtotal	395 of 1157	377 of 1344	15·9	0·86 (0·71, 1·03)
Heterogeneity: $\chi^2 = 9{\cdot}87$, 11 d.f., $P = 0{\cdot}54$; $I^2 = 0\%$				
Test for overall effect: $Z = 1{\cdot}62$, $P = 0{\cdot}11$				

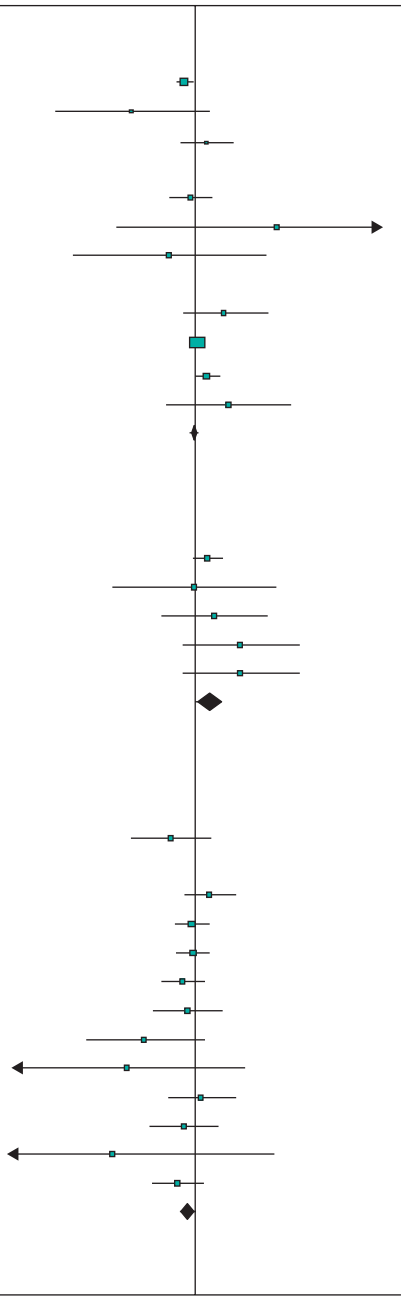

Fig. 2 Forest plot comparing effect of use of colloids *versus* crystalloids on mortality. A Peto fixed-effect model was used for meta-analysis. Odds ratios are shown with 95 per cent c.i. *Intervention group received 1000 ml hydroxyethyl starch (HES); †intervention group received 500 ml HES; ‡hypertonic saline–dextran (HSD) *versus* hypertonic saline; §HSD *versus* 0·9 per cent saline; ¶HSD 12 per cent *versus* lactated Ringer's; #HSD 6 per cent *versus* lactated Ringer's; **intervention group received 4 per cent gelatin

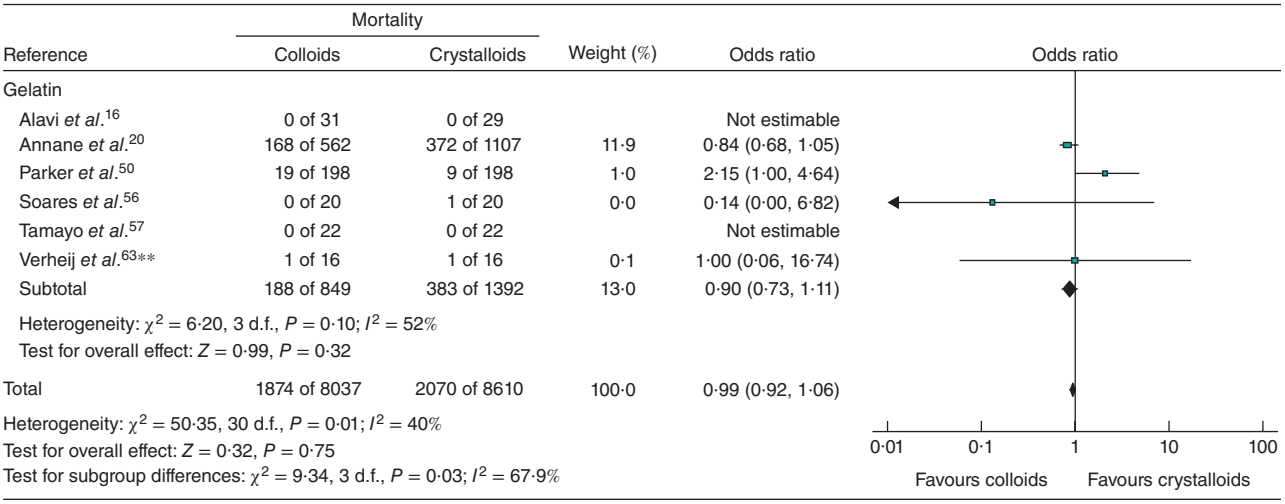

Fig. 2 Continued

reporting by 31 (53 per cent) and selective reporting by six (10 per cent). Six studies (10 per cent) had other sources of bias, including per-protocol analyses, violation of protocols and forged studies without institutional approval[13–15] A full risk of bias and GRADE assessment is provided *Table S2* (supporting information).

Based on GRADE recommendations, 18 studies (31 per cent) had no limitation, 16 (27 per cent) had serious limitations and 25 (42 per cent) had very severe limitations. Applying the recommendations, evidence for the outcomes for the primary comparison (colloid *versus* crystalloids) was graded as moderate (*Table S2*, supporting information).

Primary comparison: colloids *versus* crystalloids

Mortality

Thirty-two trials with 16 647 patients, comparing four colloids (tetrastarch, pentastarch, dextran and gelatin), were included in this analysis (*Fig. 2*). Sixteen of these trials were judged as GRADE 'limited', based on features such as serious risk of bias, imprecision and significant heterogeneity (*Table S2*, supporting information). There was no evidence that colloids increased mortality compared with crystalloids (OR 0·99, 95 per cent c.i. 0·92 to 1·06), although there was evidence of moderate heterogeneity ($I^2 = 40$ per cent). Publication bias was not observed on inspection of funnel plots (*Fig. S1*, supporting information). Exclusion of low-volume studies or low-quality studies (judged to have limitations according to GRADE criteria) did not significantly change the effect estimate (*Tables S3* and *S4*, supporting information).

Acute renal failure and acute kidney injury

Based on the results of 14 RCTs enrolling 9755 patients, colloid administration increased the risk of developing acute kidney injury or acute renal failure (OR 1·21, 95 per cent c.i. 1·07 to 1·37) (*Fig. 3*). No significant heterogeneity or publication bias was present. Exclusion of low-volume or low-quality studies did not change the effect estimate, and therefore colloids increased the odds of acute kidney injury in high-volume and high-quality RCTs (*Tables S3* and *S4*, supporting information).

Renal replacement therapy

Based on the results of nine RCTs with 11 648 patients, colloid administration increased the risk of renal replacement therapy (OR 1·35, 95 per cent c.i. 1·17 to 1·57) (*Fig. S2*, supporting information). Heterogeneity was not significant, and no publication bias was found.

The adverse effect of colloids on renal replacement therapy remained valid in the sensitivity analyses (*Tables S3* and *S4*, supporting information).

Sepsis, myocardial infarction and stroke

There was no evidence that colloid administration led to increased sepsis based on six RCTs (OR 1·01, 95 per cent c.i. 0·75 to 1·36) (*Fig. S3*, supporting information), myocardial infarction based on five trials (OR 2·32, 0·96 to 5·58) (*Fig. S4*, supporting information) or stroke based on seven RCTs (OR 1·38, 0·44 to 4·31) (*Fig. S5*, supporting information) compared with crystalloid administration. There was no evidence of between-study heterogeneity or publication bias.

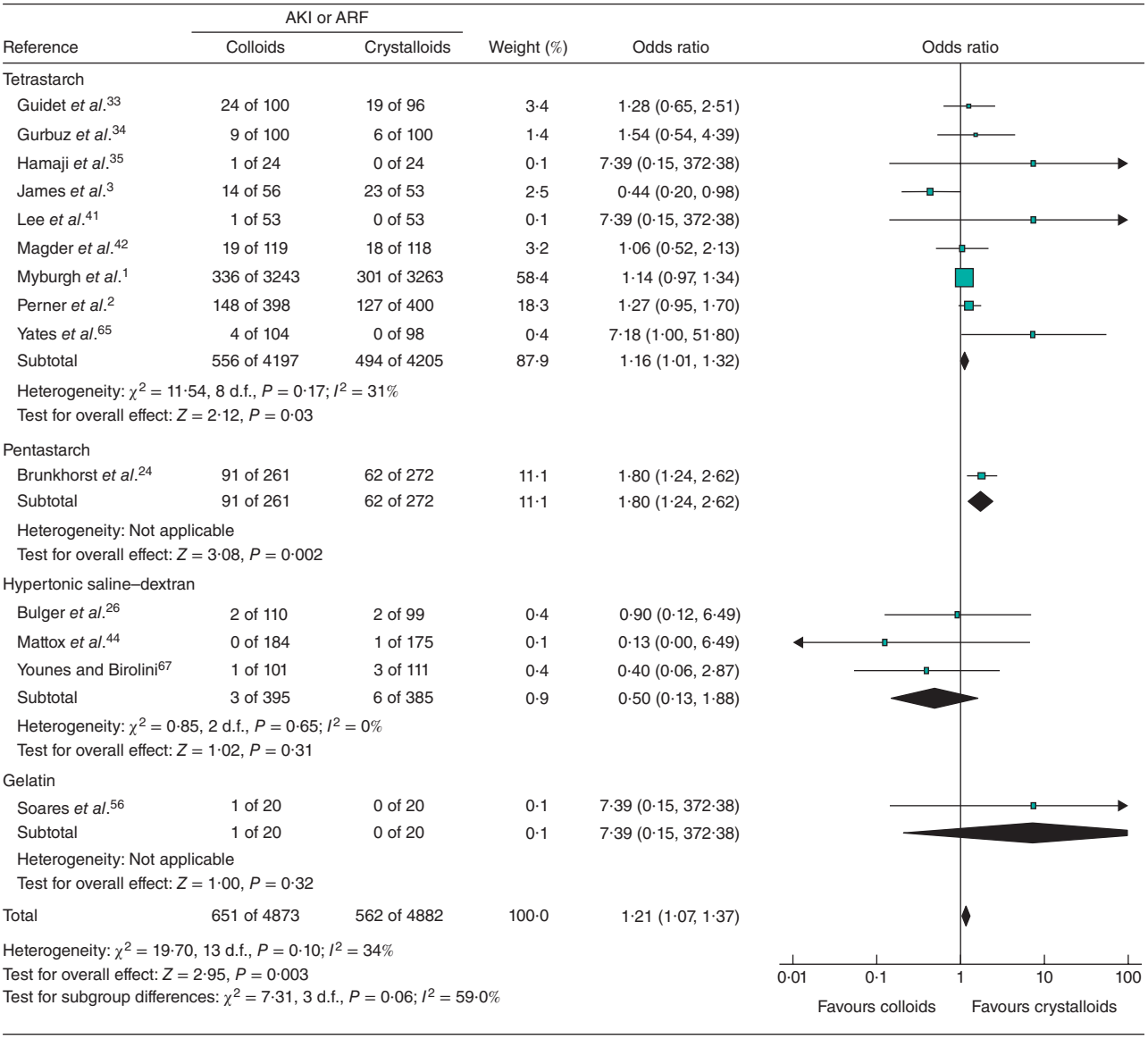

Fig. 3 Forest plot comparing effect of use of colloids *versus* crystalloids on acute kidney injury or acute renal failure. A Peto fixed-effect model was used for meta-analysis. Odds ratios are shown with 95 per cent c.i. AKI, acute kidney injury; ARF, acute renal failure

Duration of intensive care unit and hospital stay

Based on the results of 14 RCTs enrolling 10 915 patients, colloid administration increased the length of ICU stay (MD 0·40 (95 per cent c.i. 0·39 to 0·41) days) (*Fig. S6*, supporting information). Based on data from 14 trials (10 802 patients) it also increased the duration of hospital stay (MD 0·20 (0·18 to 0·21) days) (*Fig. S7*, supporting information). There was significant heterogeneity between studies reporting ICU stay ($I^2 = 83$ per cent). There was, however, no significant heterogeneity for hospital stay ($I^2 = 31$ per cent). No publication bias was found for either outcome. In analyses restricted to high-volume or high-quality studies, colloids increased the duration of ICU and hospital length of stay (*Tables S3* and *S4*, supporting information); however, heterogeneity for ICU stay remained significant.

Subgroup analyses

To determine the safety and efficacy of specific colloids, analyses were stratified according to the type of colloid administered (*Table 1*). Both tetrastarch and pentastarch increased the incidence of adverse outcomes compared

Table 1 Subgroup analyses by type of colloid

	Mortality			Acute kidney injury or acute renal failure			Renal replacement therapy		
	Event rate	Fixed-effect OR	Random-effects OR	Event rate	Fixed-effect OR	Random-effects OR	Event rate	Fixed-effect OR	Random-effects OR
Tetrastarch									
Colloids	1255 of 5600	1·01	1·06	556 of 4197	1·16	1·15	353 of 3976	1·27	1·27
Crystalloids	1199 of 5431	(0·92, 1·10)	(0·48, 1·33)	494 of 4205	(1·01, 1·32)	(0·96, 1·38)	287 of 4005	(1·08, 1·50)	(1·08, 1·50)
P		0·89	0·62		0·03	0·13		0·004	0·004
Pentastarch									
Colloids	136 of 431	1·47	1·47	91 of 261	1·80	1·81	85 of 401	1·98	1·97
Crystalloids	111 of 443	(1·08, 2·02)	(1·07, 2·03)	62 of 272	(1·24, 2·62)	(1·24, 2·65)	52 of 409	(1·35, 2·90)	(1·33, 2·92)
P		0·02	0·02		0·002*	0·002*		< 0·001	< 0·001
Dextrans									
Colloids	295 of 1157	0·86	0·86	3 of 395	0·50	0·54	Not estimable	Not estimable	Not estimable
Crystalloids	377 of 1344	(0·71, 1·03)	(0·71, 1·04)	6 of 385	(0·13, 1·88)	(0·14, 2·09)			
P		0·11	0·12		0·31	0·37			
Gelatin									
Colloids	188 of 849	0·90	1·12	1 of 20	7·39	3·15	Not estimable	Not estimable	Not estimable
Crystalloids	383 of 1392	(0·73, 1·11)	(0·56, 2·24)	0 of 20	(0·15, 372·38)	(0·12, 82·16)			
P		0·32	0·74		0·32*	0·49*			

Values in parentheses are 95 per cent c.i. *Effect estimate derived from a single study. Fixed-effect estimates were obtained by the Peto method and random-effects estimates by the Mantel–Haenszel method. OR, odds ratio.

Table 2 Subgroup analyses by clinical setting

	Mortality			Acute kidney injury			Renal replacement therapy		
	Event rate	Fixed-effect OR	Random-effects OR	Event rate	Fixed-effect OR	Random-effects OR	Event rate	Fixed-effect OR	Random-effects OR
Cardiac surgery									
Colloids	3 of 365	0·74	0·79	30 of 292	1·28	1·26	2 of 172	1·94	1·60
Crystalloids	4 of 330	(0·17, 3·32)	(0·18, 3·39)	24 of 291	(0·72, 2·26)	(0·71, 2·22)	1 of 171	(0·20, 18·71)	(0·20, 13·19)
P		0·70	0·75		0·40	0·43		0·57	0·66
General surgery									
Colloids	6 of 159	2·61	2·60	–	–	–	–	–	–
Crystalloids	2 of 152	(0·59, 11·49)	(0·59, 11·49)						
P		0·20	0·21						
Sepsis/critical care									
Colloids	1227 of 5038	1·10	1·13	627 of 4119	1·24	1·28	434 of 4149	1·37	1·43
Crystalloids	1162 of 5086	(1·00, 1·20)	(0·95,1·35)	532 of 4155	(1·09, 1·41)	(1·09, 1·51)	335 of 4190	(1·18, 1·59)	(1·15, 1·77)
P		0·06	0·16		<0·001	0·003		<0·001	0·001
Trauma									
Colloids	316 of 1260	0·91	0·91	17 of 451	0·46	0·46	2 of 56	0·62	0·62
Crystalloids	385 of 1448	(0·76,1·09)	(0·76,1·10)	29 of 438	(0·23, 0·90)	(0·23, 0·92)	3 of 53	(0·10, 3·72)	(0·10, 3·85)
P		0·31	0·32		0·02	0·03		0·60*	0·61*

Values in parentheses are 95 per cent c.i. *Effect estimate derived from a single study. Fixed-effect estimates were obtained by the Peto method and random-effects estimates by the Mantel–Haenszel method. OR, odds ratio.

with crystalloid administration. Tetrastarch increased the odds of developing acute kidney injury (9 RCTs) (OR 1·16, 95 per cent c.i. 1·01 to 1·32; $I^2 = 31$ per cent) (*Fig. 3*) and the need for renal replacement therapy (5 RCTs) (OR 1·27, 1·08 to 1·50; $I^2 = 0$ per cent) (*Fig. S2*, supporting information). Pentastarch increased mortality (4 RCTs) (OR 1·47, 1·08 to 2·02; $I^2 = 0$ per cent) (*Fig. 2*; *Fig. S8*, supporting information) and the need for renal replacement therapy (3 RCTs) (OR 1·98, 1·35 to 2·90; $I^2 = 0$ per cent) (*Fig. S2*, supporting information). Exclusion of pentastarch studies from primary analysis with or without sensitivity analyses had no effect on mortality (*Fig. S8*, supporting information). Dextran or gelatin administration did not increase the incidence of adverse outcomes compared with crystalloid administration.

To determine patient subgroups that may benefit from colloids or crystalloids, subgroup analyses were performed according to clinical setting (*Table 2*). In patients

undergoing cardiac surgery there was no evidence that colloids increased the risk of any adverse outcome compared with crystalloid administration. In patients undergoing general surgical operations there was no evidence that colloids increased mortality compared with crystalloid administration (OR 2·61, 0·59 to 11·49; $I^2 = 0$ per cent). However, these results were derived from three suitable studies comparing HES 130/0·4 *versus* control. Further comparisons in this clinical setting were not feasible owing to lack of standardized subgroups, standardized outcome reporting or comparison of interest.

Among critically ill patients or those with sepsis, colloid administration had a borderline effect on mortality (10 RCTs) (OR 1·10, 1·00 to 1·20; $I^2 = 42$ per cent) but a clear impact on acute kidney injury (5 RCTs) (OR 1·24, 1·09 to 1·41; $I^2 = 21$ per cent) and the need for renal replacement therapy (5 RCTs) (OR 1·37, 1·18 to 1·59; $I^2 = 37$ per cent) (*Table 2*).

Among patients who had experienced trauma, colloids were found to reduce the risk of developing acute kidney injury (4 RCTs) (OR 0·46, 0·23 to 0·90; $I^2 = 0$ per cent).

Secondary comparison: colloid *versus* colloid

Results of these comparisons are shown in *Table S5* (supporting information). Of the 13 included trials, 11 had serious limitations including two studies by Boldt and colleagues[13,14]. In addition, the number of trials contributing to each comparison was small, which raises significant concern regarding the validity of these results.

Discussion

The principal findings of this systematic review are that colloid administration does not increase mortality but does increase the risk of developing acute kidney injury compared with the use of crystalloid for volume replacement. Subgroup analyses demonstrated an increased risk of death and the need for renal replacement therapy associated with pentastarch, and an increased risk of acute kidney injury and the need for renal replacement therapy associated with tetrastarch. The adverse effects attributable to these interventions were observed in critically ill patients with sepsis but not in patients with traumatic injuries or those undergoing non-trauma surgery. Dextrans and gelatin were not investigated by high-quality RCTs, and it was not possible to resolve uncertainty regarding the clinical risks and benefits of these colloids from the available evidence.

The review used comprehensive search strategies, contemporary risk of bias assessments (GRADE), and assessed a wide range of outcomes in critically ill patients, injured patients and those undergoing non-trauma surgery. It identified important limitations of existing published data; 41 (69 per cent) of the 59 RCTs identified had serious limitations in terms of methodological quality. This finding, along with important subgroup interactions such as clinical setting, were considered to contribute to the heterogeneity observed in the results. After adjustment for these factors in an *a priori* sensitivity analysis, and with the exception of patients with sepsis, colloids in general resulted in no specific harm in the studied patient groups.

There are some important limitations of the present investigation. The study relied on the reported information on confounding variables that were controlled for; consistent analyses of all studies can be done only when data on individual patients are combined. The study was unable to determine whether attributes of interventions in some trials influenced the results, for example the use of 6 *versus* 10 per cent HES, molar substitution 140/0·3 *versus* 140/0·32, or dose. These factors may have contributed to the heterogeneity observed in subgroup analyses of pentastarch and tetrastarch. The value of further subgroup analyses was limited by the small numbers of patients and inconsistency of reporting of these outcomes, as noted previously[68], and these were not performed. A final limitation is that studies on albumin were excluded because any assessment of this intervention was confounded by some studies[69–72]; there are only two large well conducted RCTs – SAFE (Saline *versus* Albumin Fluid Evaluation)[73] and the recent Italian ALBIOS (Albumin for Volume Replacement in Severe Sepsis) study[74], both suggesting lack of benefit or harm to patients.

The results of the present study are also at odds with the conclusions of another recent meta-analysis[75] that included data from the recent 6S and CHEST trials; the results suggested increased mortality with HES. Serpa Neto and colleagues[75] failed to find an increase in duration of ICU stay and 28-day mortality with HES, but showed increased 90-day mortality in this subgroup. However, the analysis of 90-day mortality was essentially based on four studies, CHEST and 6S being the only high-quality trials (free from GRADE limitations); it lacked data from the recent CRISTAL and BaSES trials, which are included in the present meta-analysis. Similarly, a meta-analysis by Zarychanski and co-workers[68] reported a pooled mortality estimate in favour of crystalloid, but lacked sensitivity analyses.

The present meta-analysis was able to demonstrate patient subgroups that may benefit from either colloid or crystalloid administration. In particular, colloids resulted in an increase in acute kidney injury among patients with sepsis; conversely, they were protective against such injury in patients with traumatic injuries. This is scientifically plausible as trauma is characterized by volume loss leading to hypotension and renal ischaemia, resulting in acute kidney injury[76]. Administration of colloid in injured patients rapidly increases systemic BP and improves renal perfusion[77]. However the pathophysiology of septic acute kidney injury is different. It is not characterized by volume depletion; instead inflammation, endothelial cell injury and microcirculatory dysfunction are key mechanisms[78,79]. In such circumstances, colloids serve to increase plasma oncotic pressure sufficiently to oppose hydraulic filtration pressures within Bowman's capsule[80].

It is unclear from this review whether all colloids cause acute kidney injury in patients with sepsis as few trials have reported this outcome. Only one RCT has evaluated the impact of gelatin on acute kidney injury, whereas nine have evaluated the effect of tetrastarch, and the present analysis shows it to be nephrotoxic. There is therefore a need to conduct RCTs evaluating the renal effects of the various colloids (including gelatin) using current definitions of acute kidney injury[81].

This systematic review has demonstrated that use of colloids does not increase mortality compared with crystalloid administration in the patient groups studied. However, colloids, particularly starches, are nephrotoxic in patients with sepsis. The effect of gelatins on renal injury remains unclear owing to a lack of sufficient evidence.

Disclosure

The authors declare no conflict of interest.

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Supporting information

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

Appendix S1 Search vocabulary (Word document)

Table S1 Details of included studies (Word document)

Table S2 Risk of bias and Grading of Recommendations Assessment, Development and Evaluation of included studies for the colloid *versus* crystalloid comparison (Word document)

Table S3 Sensitivity analyses: exclusion of low-volume studies (Word document)

Table S4 Sensitivity analyses: exclusion of low-quality studies (Word document)

Table S5 Secondary comparison: colloid *versus* colloid (Word document)

Fig. S1 Funnel plot investigating publication bias for studies investigating mortality (Word document)

Fig. S2 Forest plot comparing effect of use of colloids *versus* crystalloids on the need for renal replacement therapy (Word document)

Fig. S3 Forest plot comparing effect of use of colloids *versus* crystalloids on sepsis (Word document)

Fig. S4 Forest plot comparing effect of use of colloids *versus* crystalloids on myocardial infarction (Word document)

Fig. S5 Forest plot comparing effect of use of colloids *versus* crystalloids on stroke (Word document)

Fig. S6 Forest plot comparing effect of use of colloids *versus* crystalloids on duration of intensive care unit stay (Word document)

Fig. S7 Forest plot comparing effect of use of colloids *versus* crystalloids on duration of hospital stay (Word document)

Fig. S8 Forest plot comparing effect of use of colloids *versus* crystalloids on mortality in sensitivity analyses (Word document)