Journal of Anesthesia (2020) 34:865–875
https://doi.org/10.1007/s00540-020-02832-5

ORIGINAL ARTICLE

Comparison of colloid and crystalloid using goal-directed fluid therapy protocol in non-cardiac surgery: a meta-analysis of randomized controlled trials

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Received: 19 May 2020 / Accepted: 18 July 2020 / Published online: 27 July 2020

Abstract

Purpose A few randomized controlled trials (RCTs) have compared crystalloid-based goal-directed fluid therapy (GDFT) with starch-based GDFT in patients undergoing major surgical procedures with conflicting results. In this meta-analysis, colloid-based GDFT was compared with crystalloid-based GDFT.

Methods In this meta-analysis, RCTs comparing colloid- and crystalloid-based GDFT in patients undergoing non-cardiac surgery were included. Binary outcomes were reported as risk ratio (RR) and continuous outcomes were reported as mean difference (MD) with 95% confidence interval (95% CI). PubMed, PubMed central, The Cochrane Library database and EMBASE were searched for potentially eligible trials from inception to 28 February 2020.

Results Data of 2392 patients from nine RCTs were included in this meta-analysis. Mortality at the longest available follow-up [RR (95% CI) 1.44 (0.88, 2.34); $p=0.15$], postoperative kidney dysfunction [RR (95% CI) 1.07 (0.72, 1.60); $p=0.73$], postoperative length of hospital stay [MD (95% CI) −0.29 (−1.25, 0.66) d; $p=0.55$], cardiovascular complications [RR (95% CI) 1.20 (0.50, 2.88); $p=0.68$], wound complications [RR (95% CI) 1.08 (0.76, 1.54); $p=0.66$], pulmonary complications [RR (95% CI) 0.90 (0.71, 1.140); $p=0.40$] and bleeding [RR (95% CI) 1.24 (0.77, 1.99); $p=0.37$] were similar in both the groups. Postoperative major complications were also similar between patients who received colloid and crystalloid [RR (95% CI) 0.79 (0.48, 1.29); $p=0.34$].

Conclusion Colloids in goal-directed fluid therapy protocol does not offer any benefit over crystalloid-based goal-directed fluid therapy protocol in patients undergoing major non-cardiac surgical procedure.

Keywords Colloid · Crystalloid · Goal-directed fluid therapy · Major surgery · Postoperative outcome · Major surgery · Postoperative outcome · Hemodynamic target

Introduction

Perioperative fluid therapy in patients undergoing major surgical procedure is linked with postoperative clinical outcome [1]. Both the amount and type of fluid administered in the perioperative period contribute to the postoperative outcome. 'Goal-directed fluid therapy (GDFT)' is considered to reduce postoperative mortality and morbidity in various clinical scenarios [2]. Most commonly, GDFT is achieved by optimization of stroke volume by intravenous fluid administration. A prior meta-analysis has demonstrated that GDFT reduces postoperative abdominal complications, with no demonstrable effect on mortality or length of hospital stay [3]. The majority of the randomized controlled trials (RCT) used intermittent synthetic colloid boluses such as starch or gelatin, for goal-directed management. Recently colloids, especially synthetic starches, have been challenged in critically ill patients as they offer no benefit over crystalloid, and possibly increase the need for renal replacement therapy and blood transfusion [4, 5]. Several researches were conducted on perioperative use of hydroxyethyl starch, the most commonly used synthetic colloid. A systematic review

Electronic supplementary material The online version of this article (https://doi.org/10.1007/s00540-020-02832-5) contains supplementary material, which is available to authorized users.

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and meta-analysis of 19 RCTs consisting of more than 1500 patients failed to demonstrate any effect of starch on postoperative kidney dysfunction. It also failed to demonstrate any benefit of colloid over crystalloid [6]. Moreover, use of starch was associated with kidney dysfunction both in critically ill patients and cardiac surgical patients which needs serious attention [7, 8].

Recently, a number of RCTs have compared crystalloid-based GDFT with starch-based GDFT in patients undergoing major surgical procedures, with a few RCTs showing benefit of starch over crystalloid, and the rest showing no benefit [8–15]. However, the majority of the RCTs had small samples. Hence, this systematic review and meta-analysis of RCTs was planned to identify whether colloid-based GDFT was superior to crystalloid-based GDFT.

Method

The PRISMA guidelines were followed for conducting and reporting of this meta-analysis and systematic review [16]. The protocol of this meta-analysis was registered in PROSPERO (CRD42019131745).

Eligibility criteria

Published RCTs comparing colloid-based GDFT with crystalloid-based GDFT regimen in adult patients undergoing non-cardiac surgeries were included in this meta-analysis. RCTs, which used any synthetic colloid such as starch, gelatin or dextran as intravenous fluid boluses for goal-directed therapy, were included in this meta-analysis. Any validated method of intravascular volume optimization such as measurement of cardiac output and/ or cardiac index, stroke volume variation, pulse pressure variation, and corrected flow time were considered as 'GDFT'. RCTs that reported at least one postoperative complication were included in this meta-analysis.

Exclusion criteria

RCTs in patients undergoing cardiac surgery were not included in this meta-analysis.

Information sources

PubMed, PubMed central, The Cochrane Library database and EMBASE were searched for potentially eligible trials from inception to 28 February 2020. No language restriction was applied in the search strategy. We also manually searched references of the previously published relevant meta-analyses.

Search strategy

The following keywords were used to search the databases: "*randomized controlled trial, randomized clinical trial, colloid, crystalloid, goal directed therapy, goal directed fluid therapy*". Details of PubMed/ PubMed Central, The Cochrane Library database and EMBASE search strategy have been provided in appendix 1.

Study selection

Title and abstracts of the possibly eligible trials were independently searched by two authors (AT and SM). Then, full texts of the potentially eligible trials were retrieved and assessed for inclusion in this meta-analysis. Any disagreement between the two review authors were discussed and solved in consultation with the third review author (SB).

Data collection process

Required data from the eligible RCTs were extracted by two independent authors (AT and SM) from the included trials and all data were initially tabulated in a Microsoft Excel™ (Microsoft Corp., Redmond, WA) data sheet. All data were cross-checked by the third review author (SB).

Data items

The following data were retrieved from the full text: first author, year of publication, country where work was done, sample size, inclusion criteria of the patients, hemodynamic optimization target (e.g. stroke volume, pulse pressure variation, cardiac index, corrected flow time etc.), details of colloid or crystalloid administered, blood loss, postoperative outcome (major complications, postoperative organ dysfunction, postoperative intensive care unit (ICU) admission, postoperative hospital and ICU length of stay and mortality at the longest reported follow-up).

Risk of bias in individual studies

The methodological quality of the included RCTs were assessed by two independent authors (SM and SB). The following methodological questions were searched from the studies as per the Cochrane methodology (yes, no or uncertain): method of randomization, allocation concealment, blinding of the participants and personnel, blinding

of outcome assessment, incomplete data reporting, selective reporting and any other bias [17].

Summary measures and synthesis of results

Predefined primary outcome of this meta-analysis was '*number of patients with at least one postoperative complication*'. Predefined secondary outcomes were 'mortality at longest available follow-up', incidence of acute kidney injury (AKI), length of hospital stay, any reported organ specific complications (cardiovascular complications, wound complications, pulmonary complications and bleeding) and incidence of major postoperative complications (as defined by the trial authors).

For a continuous variable, the mean and standard deviation (SD) values were extracted from both arms of the trial, a mean difference (MD) was computed at the study level, and a weighted mean difference was computed to pool the results across all RCTs. If the values were reported as median and an inter-quartile range or total range of values, the mean value was estimated from a previously described method [18]. The risk ratio (RR) for each trial and pooled RR using the inverse variance method were calculated for binary variables. All statistical variables were calculated with 95% confidence interval (95% CI). The Q-test was used to analyze the heterogeneity of trials. Considering the possible heterogeneity due to study design and patients' population, we used a random effect model for all pooled analysis. Pooled analysis was conducted in RevMan software (Review Manager (RevMan) [Computer program]. Version 5.3. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014). Publication bias was tested by Egger's regression test. A meta-regression was also planned to assess the effects of sample size, baseline risk of events in control group patients and year of publication on postoperative outcome in case more than ten trials are included. Missing outcome data were estimated by *mice* package in R (R Development Core Team, 2010; R Foundation for Statistical Computing, Vienna, Austria) by predictive mean matching. Each outcome was assessed by GRADE (Grading of Recommendations, Assessment, Development and Evaluations) methodology which considered risk of bias, imprecision, inconsistency, indirectness and publication bias to determine the 'quality of evidences' [19].

Results

Initial database searching revealed 8564 articles and after duplicate removal and screening $n = 319$ relevant articles were assessed for inclusion in this meta-analysis. Searching of the other sources revealed 18 other articles. Finally, the data of 2392 patients from nine RCTs were included in this meta-analysis [9–15, 20, 21]. A PRISMA flow diagram showing the process of study selection has been depicted in Fig. 1. One RCT was not included because it included no outcome that could be pooled from it [22]. Characteristics of the included trials including the amount of study fluid received in each group at individual trial have been reported in Table 1. The review authors' judgment about each risk of bias in the individual trail has been depicted in Fig. 2.

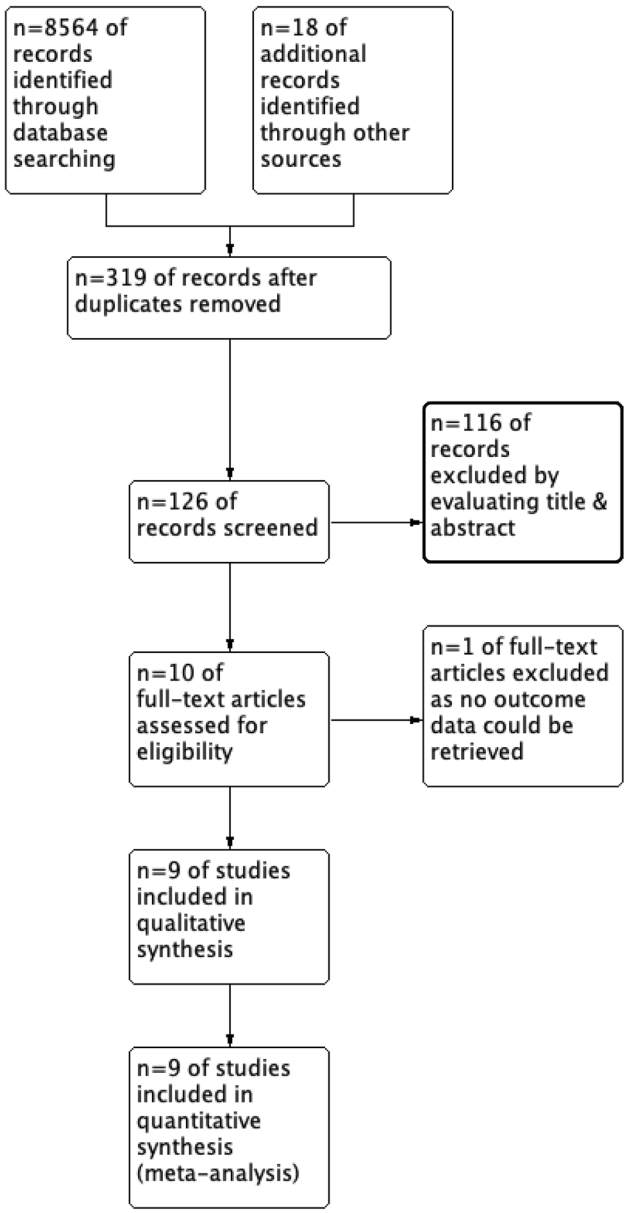

Fig. 1 PRISMA flow diagram showing the study selection procedure

Our original plan was to analyze the 'number of patients with at least one postoperative complication' as primary outcome. However, as no study explicitly reported this outcome, the rest of the prespecified additional outcomes were analyzed. Eight of the included trials reported postoperative

Table 1 Characteristics of the included trials: data reported as mean (SD) or median (IQR), as available

Author	Participants	Sample size/ female	Colloid group		Crystalloid group		Hemodynamic goal	Primary outcome	Blood loss		Follow-up duration
			Fluid	Amount[#]	Fluid protocol	Amount[#]			Colloid	Crystalloid	
Kabon [9]	Adult patients scheduled for open or laparoscopic-assisted abdominal surgery expected to last at least 2 h, and ASA PS I–III, had a body mass index of less than 35 kg/m^2	1057/ 510	6% 130/0.4 HES	1 [0.5, 1.5] l	Ringer's lactate	3.2 [2.3, 4.4]	Esophageal Doppler	Postoperative morbidity, defined by a composite of major complications	250 [100, 500]	250 [100, 500]	30 days
Tyagi [11]	Adult patients scheduled for major orthopedic surgery under GA with anticipated blood loss > 200–300 mL were included	38/ 15	6% 130/0.4 HES	689 (394) ml	Ringer's lactate	1211 (758)	SVV optimization from Flo Trac	Postoperative kidney dysfunction	Not reported		Hospital discharge or 16th postoperative day
Joosten [10]	Adult patients scheduled to undergo GA for elective open abdominal surgery expected to last at least 3 h	160/ 64	Balanced 6% 130/0.4 HES	2.9 [1.9, 3.9] ml/kg/h	Plasmalyte	4 [2.6, 6.2] ml/kg/h	SV optimization by closed loop system with 100 ml boluses	POMS at POD2	2.1 [1.1–4.1]l	1.7 [0.9–3.3] l	30- days

Table 1 (continued)

Author	Participants	Sample size/ female	Colloid group		Crystalloid group		Hemodynamic goal	Primary outcome	Blood loss		Follow-up duration
			Fluid	Amount[#]	Fluid protocol	Amount[#]			Colloid	Crystalloid	
Feldheiser [12]*	Adult patients with primary ovarian cancer undergoing cytoreductive surgery	48/48	Balanced 6% 130/0.4 HES	91%	Balanced crystalloid	62%	SV/FTc optimized from esophageal Doppler	Amount of intravenous fluid administered	Not reported		Up to 3 months
Yates [13]	Medium to high-risk patients undergoing elective colorectal surgery	202/85	Balanced 6% 130/0.4 HES	1875 [1500-3000] ml	Balanced crystalloid	3175 [2000-3700] ml	Target SVV < 10% derived from LiDCO rapid system	Gastrointestinal smorbidity at day 5 after surgery	250 [50- 700] ml	200 [100-620] ml	Till hospital discharge
Zhang [14]	Adult patients who were undergoing elective gastrointestinal surgeries with an anticipated blood loss of less than 500 ml	60/ 18[^]	6% 130/0.4 HES	865 (297) ml	Ringer's lactate	1853 (381) ml	PPV	Postoperative length of hospital stay	265 (46.2)	256.51(39.9)	Till hospital discharge
Senagore [15]	Adult patients undergoing elective laparoscopic segmental colectomy	64[@]	6% 130/0.4 HES	389 (287) ml	Ringer's lactate	863 (850) ml	SV optimization by esophageal Doppler	Postoperative length of hospital stay	Not reported		Till hospital discharge
Lindroos [20]	Adult patients scheduled for elective primary neurosurgery in the prone position	30/ 17	6% 130/0.4 HES	865 (297) ml	Ringer's acetate	1853 (381) ml	SV optimization by FloTrac	Hemodynamic variables and coagulation parameters	216 (160)	201 (278)	Till hospital discharge

Table 1 (continued)

Author	Participants	Sample size/ female	Colloid group		Crystalloid group		Hemodynamic goal	Primary outcome	Blood loss		Follow-up duration
			Fluid	Amount[#]	Fluid protocol	Amount[#]			Colloid	Crystalloid	
Futier [21]	Adult patients undergoing elective or nonelective abdominal surgery under GA with a duration of 2 h or longer and who had an intermediate to high risk of developing postoperative complications	826/ 91	6% 130/0.4 HES	1000 (750-1500) ml	0.9% Saline	1250 (750-2000)	SV optimization	Composite primary outcome of death or major complications	Not reported		28- day

SV stroke volume, *GA* general anaesthesia, *HES* hydroxyethyl starch, *PPV* pulse pressure variation, *SVV* stroke volume variation, *FTc* corrected flow time, *ASAPS* american society of anesthesiologists' physical status

*Authors reported % of patients received maximum dose limit of 50 ml/kg of study fluid

[#]Amount of fluid study administered for hemodynamic optimization

@ 42 patients were included in this meta-analysis

^40 patients were included in this meta-analysis and 12 were female

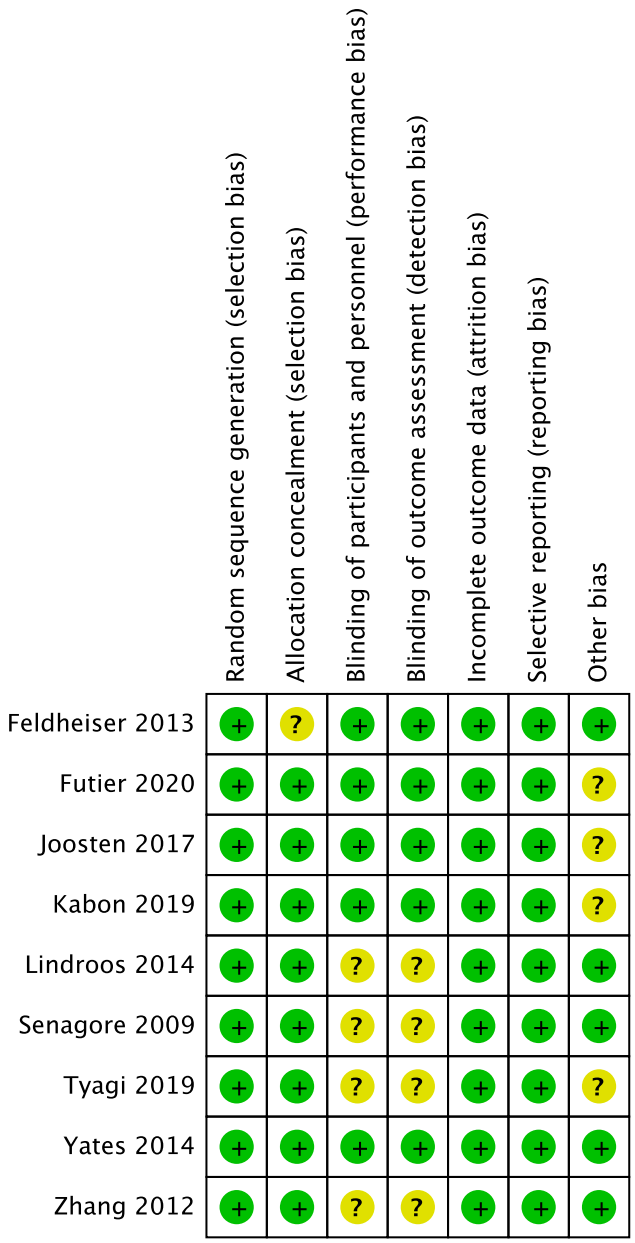

Fig. 2 Risk of bias summary: review authors' judgments about each risk of bias item for each included study

mortality, and mortality at longest available follow-up was found to be similar in both the groups [RR (95% CI) 1.44 (0.88, 2.34); $p=0.15$, $I^2=0.0\%$; $n=2322$; quality of evidence: low]. Standard deviations of length of hospital stay were not reported for two trials [11, 13] and those were estimated by multiple imputation with predictive mean matching. Postoperative kidney dysfunction was also similar in both the groups [RR (95% CI) 1.07 (0.72, 1.60); $p=0.73$; $I^2=29\%$; quality of evidence: low]. Postoperative hospital length of stay was also similar in the two groups [MD (95% CI) −0.29 (−1.25, 0.66) day; $p=0.55$, $I^2=82\%$; $n=2392$, quality of evidence: moderate]. Forest plots showing RR and MD of mortality and length of hospital stay at study level and pooled analysis level have been depicted in Fig. 3. The incidence of postoperative cardiovascular complications was similar between patients who received colloid and crystalloid [RR (95% CI) 1.20 (0.50, 2.88); $p=0.68$; $I^2=56\%$; quality of evidence: very low]. Postoperative wound complication rate [RR (95% CI) 1.08 (0.76, 1.54); $p=0.66$; $I^2=1\%$; quality of evidence: very low], pulmonary complications [RR (95% CI) 0.90 (0.71, 1.14); $p=0.40$; $I^2=47\%$; quality of evidence: low] and bleeding [RR (95% CI) 1.24 (0.77, 1.99); $p=0.37$; $I^2=7\%$; quality of evidence: very low] were also similar between both the groups. Four RCTs reported postoperative major complications and it was found to be similar between patients who received colloid and crystalloid [RR (95% CI) 0.79 (0.48, 1.29); $p=0.34$; $I^2=62\%$; quality of evidence: very low]. The summary of findings as per GRADE methodology has been provided in Fig. 4. Quality of evidences for 'length of hospital stay', downgraded because of significant heterogeneity, and 'postoperative kidney dysfunction', downgraded because of different definitions of 'kidney dysfunction', were used in the different trials (Table 2).

A sensitivity analysis was performed excluding the study of Futier et al. [21], as 0.9% saline was used as opposed to balanced salt solution and fluid therapy protocol was used in the postoperative period. However, mortality at longest follow-up ($p=0.53$), length of hospital stay ($p=0.76$) and postoperative kidney dysfunction ($p=0.45$) remained similar in both the groups. Another sensitivity analysis was performed excluding the studies by Lindroos et al. [20] and Tyagi et al. [11], as these RCTs were conducted in a non-abdominal surgical setting. Mortality at the longest follow-up ($p=0.15$), length of hospital stay ($p=0.45$) and postoperative kidney dysfunction ($p=0.71$) remained similar in both the groups even in this sensitivity analysis. Lastly, we did another sensitivity analysis excluding the study of Yates et al. [13] as it included only severe kidney dysfunction requiring dialysis; we found that postoperative kidney dysfunction was similar ($p=0.70$).

Discussion

We found no benefit of colloid-based GDFT over crystalloid-based goal-directed fluid therapy in terms of postoperative mortality, length of hospital stay or any other organ-specific complications. The incidence of postoperative kidney dysfunction was also similar in both the groups.

Goal-directed fluid therapy in major non-cardiac surgery is a long-debated matter in perioperative medicine. A meta-analysis of 41 RCTs reported that colloid-based goal-directed fluid therapy was associated with less postoperative

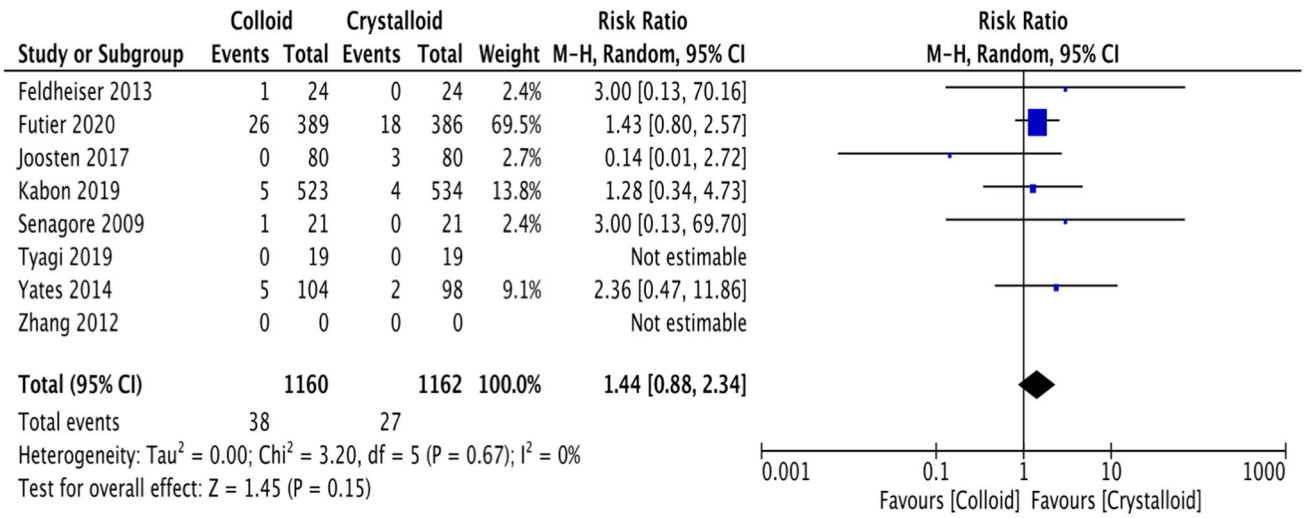

Fig. 3 Forest plot showing the risk ratio of 'mortality at longest follow-up' (upper) and mean difference of 'postoperative length of hospital stay' (lower) at individual study level and pooled analysis level

wound infection, abdominal complications and hypotension over conventional fluid therapy [3]. However, no mortality benefit was obtained in that meta-analysis. Another subsequent meta-analysis of 95 RCTs, including both cardiac and non-cardiac surgical patients, reported that GDFT was associated with significant mortality benefit over conventional fluid therapy [22].

Although colloid-based GDFT was compared with conventional fluid therapy in a number of RCTs, only a few authors compared crystalloid boluses for GDFT with colloid-based GDFT, generating conflicting results. Kabon et al. reported that postoperative complications including kidney dysfunction were similar between patients undergoing moderate- to high-risk abdominal surgery, in patients receiving colloid or crystalloid within a goal-directed fluid therapy protocol [9]. In contrast, Joosten et al. reported a reduction in postoperative morbidity and complications with the use of colloid-based GDFT [10]. Our meta-analysis failed to find any benefit of colloid in terms of postoperative complications or any organ-specific morbidity. Our finding probably highlights the fact that the amount of fluid administered during surgery is more important than whether colloid or crystalloid is used.

Nowadays, the use of synthetic colloids, especially starches, is being discouraged in critically ill patients due to increased

Fig. 4 Summary of findings table for all outcomes as per GRADE ▶ methodology Comparison of colloid and crystalloid using goal-directed fluid therapy protocol: a meta-analysis of randomized controlled trials

Colloid compared to Crystalloid for goal directed fluid therapy protocol

Patient or population: goal directed fluid therapy protocol
Setting:
Intervention: Colloid
Comparison: Crystalloid

Outcomes	№ of participants (studies) Follow up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Crystalloid	Risk difference with Colloid
Mortality at longest follow-up	2322 (8 RCTs)	⨁⨁◯◯ LOW [a,b,c]	**RR 1.44** (0.88 to 2.34)	23 per 1,000	**10 more per 1,000** (3 fewer to 31 more)
Length of hospital stay	2392 (9 RCTs)	⨁⨁⨁◯ MODERATE [a,b]	-	The mean length of hospital stay was **0**	MD **0.29 lower** (1.25 lower to 0.66 higher)
Kidney Dysfunction	2232 (5 RCTs)	⨁⨁◯◯ LOW [a,b,d]	**RR 1.07** (0.72 to 1.60)	85 per 1,000	**6 more per 1,000** (24 fewer to 51 more)
Cardiac Complications	2276 (6 RCTs)	⨁◯◯◯ VERY LOW [a,b,c,d]	**RR 1.20** (0.50 to 2.88)	53 per 1,000	**11 more per 1,000** (26 fewer to 99 more)
Wound Complications	1219 (5 RCTs)	⨁◯◯◯ VERY LOW [a,b,d,e]	**RR 1.08** (0.76 to 1.54)	89 per 1,000	**7 more per 1,000** (21 fewer to 48 more)
Pulmonary Complications	2276 (6 RCTs)	⨁⨁◯◯ LOW [a,b]	**RR 0.90** (0.71 to 1.14)	107 per 1,000	**11 fewer per 1,000** (31 fewer to 15 more)
Major Bleeding	2236 (5 RCTs)	⨁◯◯◯ VERY LOW [a,b,c,d]	**RR 1.24** (0.77 to 1.99)	33 per 1,000	**8 more per 1,000** (8 fewer to 33 more)
Major Postoperative Complications	1459 (4 RCTs)	⨁◯◯◯ VERY LOW [a,b,c,d]	**RR 0.79** (0.48 to 1.29)	202 per 1,000	**42 fewer per 1,000** (105 fewer to 59 more)

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; **RR:** Risk ratio; **MD:** Mean difference

GRADE Working Group grades of evidence
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

Explanations

a. Lack of blinding in many studies
b. Different inclusion criteria and risk profile of the patients
c. Wide confidence interval
d. Outcome definition is variable
e. small number of patients

Table 2 Definition of acute kidney injury in different trials

Author	Definition
Kabon [9]	KDIGO definition
Tyagi [11]	Urinary NGAL and KDIGO definition
Joosten [10]	KDIGO definition
Feldheiser [12]	Not reported
Yates [13]	Required CVVH or dialysis
Zhang [14]	Not reported
Senagore [15]	Not reported
Lindroos [20]	Not reported
Futier [21]	AKI > stage I, KDIGO

KDIGO kidney disease improving global outcomes, *NGAL* neutrophil gelatinase- associated lipocalin, *CVVH* continuous veno-venous hemofiltration

requirement of renal replacement therapy and possibly increased mortality [4, 23]. In surgical patients, the clinical effects of synthetic colloid are less clear. A retrospective study reported increased incidence of acute AKI in orthoptic liver transplant patients with the use of starch when compared to human albumin [24]. A meta-analysis by Ramussen et al. reported higher postoperative bleeding with the use of starch in comparison to crystalloid in non-cardiac surgery patients [25]. In another well-conducted meta-analysis of 13 RCTs, Gilles et al. reported no differences in the incidence of postoperative AKI [6]. It is worth mentioning that the included trials were small in sample size and the event rate of AKI was also low; hence, these findings require validation in large RCTs. In our meta-analysis, we have found that incidence of postoperative kidney dysfunction was not higher in patients who received colloid as compared to crystalloid. As patients undergoing routine surgery are rarely septic, starches may have minimal detrimental effect on kidney function in this setting.

The length of hospital stay was similar in our analysis irrespective of the type of intravascular fluid used. Som et al. [3] also reported a similar postoperative hospital length of stay with the use of colloid-based GDFT as opposed to standard fluid therapy. However, use of colloid-based fluid therapy reduced the number of patients with at least one postoperative complication. Despite the common concern of coagulopathy [26], in our meta-analysis, we did not find any increased incidence of postoperative bleeding with the use of starch.

Strength and limitation

The most important strength of this meta-analysis is the absence of any statistical heterogeneity in 'postoperative mortality', which is an important patient-centric outcome. However, this meta-analysis has several limitations. Other than postoperative mortality, significant statistical heterogeneity was found in most of the other outcomes. Moreover, clinical heterogeneity is also possible because of different inclusion criteria and fluid therapy protocol. Hence, the quality of evidences was downgraded to 'low' to 'very low'. Event rates in the postoperative outcomes were also small, which could again contribute to the downgrading of the quality of the evidences.

Conclusion

The use of colloids in goal-directed fluid therapy protocol does not offer any benefit over crystalloid-based goal-directed fluid therapy protocol in patients undergoing major non-cardiac surgical procedures. However, no increased incidence of kidney dysfunction was found with the use of colloid.

Compliance with ethical standard

Conflict of interest None declared.

Appendix 1: Details of search strategy

1. PubMed/PubMed Central

("colloids" [pharmacological action] OR "colloids" [MeSH terms] OR "colloids" [all fields] OR "colloid" [all fields]) AND ("crystalloid solutions" [MeSH terms] OR ("crystalloid" [all fields] AND "solutions" [all fields]) OR "crystalloid solutions" [all fields] OR "crystalloid" [all fields]).

("goals" [MeSH terms] OR "goals" [all fields] OR "goal" [all fields]) AND directed [all fields] AND ("therapy" [subheading] OR "therapy" [all fields] OR "therapeutics" [MeSH terms] OR "therapeutics" [all fields]).

("goals" [MeSH terms] OR "goals" [all fields] OR "goal" [all fields]) AND directed [all fields] AND ("fluid therapy" [MeSH terms] OR ("fluid" [all fields] AND "therapy" [all fields]) OR "fluid therapy" [all fields]).

("goals" [MeSH terms] OR "goals" [all fields] OR "goal" [all fields]) AND directed [all fields] AND ("fluid therapy" [MeSH terms] OR ("fluid" [all fields] AND "therapy" [all Fields]) OR "fluid therapy" [all fields]).

("goals" [MeSH terms] OR "goals" [all fields] OR "goal" [all fields]) AND directed [all fields] AND ("therapy" [Subheading] OR "therapy" [all fields] OR "therapeutics" [MeSH terms] OR "therapeutics" [all fields]) AND major [all fields] AND ("surgery" [subheading] OR "surgery" [all fields] OR "surgical procedures, operative" [MeSH terms] OR ("surgical" [all fields] AND "procedures" [all fields] AND "operative" [all fields]) OR "operative surgical procedures" [all fields] OR "surgery" [all fields] OR "general surgery"[

MeSH terms] OR ("general" [all fields] AND "surgery" [all fields]) OR "general surgery" [all fields]).

2. EMBASE

"colloid:ti,ab,kw" Or 'goal directed fluid therapy' Or 'crystalloid' Or 'goal directed therapy' And 'randomized controlled trial' Or "randomized AND trial".

3. CENTRAL database

(colloid):ti,ab,kw Or (crystalloid):ti,ab,kw Or (goal directed fluid therapy):ti,ab,kw Or (goal directed therapy):ti,ab,kw And ("randomized clinical trial"):ti,ab,kw Or ("randomized controlled trial"):ti,ab,kw.

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