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Hydroxyethyl Starch for Fluid Management in Patients Undergoing Major Abdominal Surgery: A Systematic Review With Meta-analysis and Trial Sequential Analysis

Joris Pensier, MD,*† Lucas Deffontis, MD,*† Amélie Rollé, MD,*† Yassir Aarab, MD,*† Mathieu Capdevila, MD,*† Clément Monet, MD,*† Julie Carr, MD,*† Emmanuel Futier, MD, PhD,‡ Nicolas Molinari, PhD,§ Samir Jaber, MD, PhD,*†|| and Audrey De Jong, MD, PhD*†||

*Anesthesiology and Intensive Care, Anesthesia and Critical Care Department B, Saint Eloi Teaching Hospital, Montpellier Cedex 5, France;

† Département d'Anesthésie-Réanimation B, Centre Hospitalier Universitaire Montpellier, Montpellier, France;

‡ Centre Hospitalier Universitaire Clermont-Ferrand, Département de Médecine Périopératoire, Anesthésie et Réanimation, Clermont-Ferrand, France;

§ Department of Statistics, University of Montpellier Lapeyronie Hospital, UMR 729 MISTEA, Montpellier, France; and

// Anesthesiology and Intensive Care, Anesthesia and Critical Care Department B, Saint Eloi Teaching Hospital, PhyMedExp, University of Montpellier, INSERM U1046, CNRS UMR 9214, Montpellier Cedex 5 Montpellier, France.

J. Pensier and L. Deffontis contributed equally to the study.

Address correspondence to:

Audrey De Jong, MD, PhD, Intensive Care Unit, Anaesthesia and Critical Care Department, Saint Eloi Teaching Hospital, University Montpellier 1, 80 Ave Augustin Fliche, 34295 Montpellier Cedex 5, France.

Address e-mail to:

a-de_jong@chu-montpellier.fr.

GLOSSARY

AKI = acute kidney injury; ASA = American Society of Anesthesiologists; CI = confidence interval; *df* = degrees of freedom; HES = hydroxyethyl starch; *I*² = heterogeneity statistic; KDIGO = Kidney Disease Improving Global Outcomes; M-H = Mantel-Haenszel; MD = mean difference; PRISMA = Preferred Reporting Items for Systematic Reviews and Meta-Analyses; PROSPERO = International Prospective Register of Systematic Reviews; RBC = red blood cell; RCT = randomized controlled trial; RR = relative risk; RRI = relative risk increase; RRR = relative risk reduction; RRT = renal replacement therapy; SV = stroke volume; TSA = trial sequential analysis

METHODS:

In this meta-analysis and TSA, we searched for randomized controlled trials (RCTs) comparing intraoperative HES intravascular volume replacement to crystalloid intravascular volume replacement in adult patients undergoing major abdominal surgery. Primary outcome was 30-day AKI, defined as a binary outcome according to Kidney Disease Improving Global Outcomes (KDIGO) criteria, combining stages 1, 2, and 3 into an AKI category versus no AKI category (stage 0). Secondary outcomes included rates of intraoperative blood transfusion and postoperative intra-abdominal complications. We used random effects models to calculate summary estimates. We used relative risk (RR) as summary measure for dichotomous outcomes, with corresponding 95% confidence intervals (CIs) for the primary outcome (P value $<.05$ was considered statistically significant) and 99% CI after Bonferroni correction for the secondary outcomes (P value $<.01$ was considered statistically significant).

RESULTS:

Seven RCTs including 2398 patients were included. HES intravascular volume replacement was not associated with an increased risk of 30-day AKI (RR = 1.22, 95% CI, 0.94–1.59; P = .13), when compared to crystalloid intravascular volume replacement. According to TSA, this analysis was underpowered. HES intravascular volume replacement was associated with higher rates of blood transfusion (RR = 1.57 99% CI, 1.10–2.25; P = .001), and similar rates of postoperative intra-abdominal complications (RR = 0.76 99% CI, 0.57–1.02; P = .02).

CONCLUSIONS:

In this meta-analysis to focus on HES intravascular volume replacement in major abdominal surgery, HES intravascular volume replacement was not associated with a higher risk of 30-day AKI when compared to crystalloid intravascular volume replacement. However, CI and TSA do not exclude harmful effects of HES intravascular volume replacement on the renal function

Crystalloid solutions are the most commonly used perioperative fluids.¹ Crystalloid solutions accumulate in tissues and are inclined to promote edema and prolonged recovery.^{2,3} Contrary to crystalloids, colloids produce faster and more persistent hemodynamic effects on account of their higher oncotic pressure.⁴ Nevertheless, colloids are disparaged for their suspected adverse effects on coagulation by reducing clot formation and strength, implying hematological complications.⁵ In addition, colloids might also impair kidney function.⁶ This is the reason that in 2013, the Food and Drug Administration issued warnings about a risk of death and acute kidney injury (AKI) with hydroxyethyl starch (HES) solutions in critically ill patients, while the European Medicine Agency prohibited them in intensive care units.⁷ However, these data were obtained exclusively from critically ill patients.^{8,9} Applying them directly to a surgical population needs a specific evaluation, especially in the modern area of goal-directed fluid strategies.¹⁰

In major abdominal surgery, fewer postoperative complications have been reported with a colloid-based goal-directed fluid strategy compared to a goal-directed fluid strategy using only crystalloids.¹¹ However, more AKI,¹² altered coagulation and subsequent bleeding and

blood transfusion^{13,14} have also been reported when using a colloid-based goal-directed fluid strategy during the perioperative period.

We hypothesized that, similarly than in critically ill patients, the use of HES during major abdominal surgery was associated with increased 30-day AKI. We also hypothesized that the use of HES would be associated with increased renal replacement therapy (RRT), increased 30-day mortality, increased intraoperative red blood cell (RBC) transfusion, increased intraoperative need for norepinephrine, and decreased 30-day postoperative intra-abdominal complications. Therefore, we designed this systematic review with meta-analysis of randomized controlled trials (RCTs) and trial sequential analysis (TSA) to assess the effect of a HES intravascular volume replacement strategy versus a crystalloid intravascular volume replacement strategy on AKI, RRT, 30-day mortality, intraoperative RBC transfusion, intraoperative need for norepinephrine, and 30-day postoperative intra-abdominal complications in patients undergoing major abdominal surgery.

METHODS

We conducted a systematic review and meta-analysis of RCTs comparing HES versus crystalloids for major abdominal surgery, in accordance with the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) statement.¹⁵ The meta-analysis was registered on the International Prospective Register of Systematic Reviews (PROSPERO) register of systematic review (CRD42020163450).

Search Strategy

We performed a computerized search of MEDLINE (2000–2020), the Cochrane Centre Register of Controlled Trials (CENTRAL) (2000–2020), and Web of Science (2000–2020) for RCTs comparing a HES intravascular volume replacement strategy to a crystalloid intravascular volume replacement strategy.

We included non-English publications. We searched abstracts of selected conferences from 2010 to 2020, including those of the American Society of Anaesthesiologists, the Canadian Anaesthesiologists' Society, the International Anaesthesia Research Society, the American Thoracic Society, the European Society of Anaesthesiology and the "Société Française d'Anesthésie Réanimation."

For the bibliographic review, keywords ("Colloid," "Hydroxyethyl starches," "HES," "Abdominal surgery," "Crystalloid," "Intravascular volume replacement," and "Fluid-loading") and medical subject headings ("Perioperative care" and "adult") were used in our search strategy. References in the retrieved articles were also examined for relevant publications.

We identified and deleted any duplicate papers. All potential eligible papers were retrieved in full.

Selection Criteria and Outcome Measures

We screened for relevant RCTs that enrolled adult patients undergoing major abdominal surgery, defined as open or laparoscopic-assisted abdominal surgery expected to last at least 2 hours and associated with a high risk of postoperative complications.^{12,16}

Then we made a quantitative synthesis performing a meta-analysis and systematic review. The main outcome was all stages AKI within 30 days (30-day AKI) defined as a binary outcome according to Kidney Disease Improving Global Outcomes (KDIGO) criteria, ¹⁷ combining stages 1, 2, and 3 into an AKI category versus no AKI category (stage 0). Whenever data on 30-day AKI were not available, we selected 28-day AKI or 14-day AKI as end point, in this order. The secondary outcomes were 30-day need for RRT, to assess postoperative renal failure, 30-day mortality, intraoperative RBC transfusion and intraoperative need for norepinephrine to assess potential impaired coagulation and subsequent bleeding and transfusion, and 30-day postoperative intra-abdominal complications (defined as anastomotic leakage, intraabdominal sepsis, or reoperation). The composite outcome was deemed appropriate, as the 3 components of the composite outcome “30-day postoperative intra-abdominal complications” (anastomotic leakage, abdominal sepsis, and reoperation) may have similar severity, frequency and might equally be affected by the intervention. ^{18,19} Severity and frequency of anastomotic leakage, intra-abdominal sepsis, or reoperation may be considered equivalent, as a reoperation is often driven by an intra-abdominal sepsis, consecutive to an anastomotic leakage,²⁰ and as an anastomotic leakage often triggers an intra-abdominal sepsis followed by a reoperation.^{20,21} By avoiding massive fluid administration, the colloids may similarly decrease the 3 components of the composite outcome: primary anastomotic leakage, second, the rate of intra-abdominal sepsis (because of less anastomotic leakage), and third, reoperation (because of less anastomotic leakage and intra-abdominal sepsis).^{20,21}

Data Collection and Analysis

First, 2 authors (L.D. and J.P.) independently screened the retrieved studies by title and then by abstract for exclusion. They assessed the full text of the possible relevant studies for inclusion and exclusion criteria. Disagreement was resolved by discussion and arbitrated, if necessary, by a third author (A.D.J.). Data were then added to an excel database, specifically designed for this review and analyzed in RevMan 5.3 software and TSA viewer version 0.9.5.10 Beta.²²

Statistical Analysis

Data were extracted as they were reported in the original paper or based on the answers of the authors to our queries. Queries were sent via e-mail to corresponding authors of each study included, and data on both primary and secondary outcomes were asked when not reported in the original paper. Included studies were appraised for their risk of bias by 3 independent authors (J.P., L.D., A.D.J.) using the Cochrane Collaboration’s tool for assessing risk of bias in RCTs. We used random effects models to calculate summary estimates.²³ We used relative risk (RR) as the summary measure for dichotomous outcomes, and mean difference (MD) as the summary measure for continuous outcomes, with corresponding confidence intervals (CIs). Statistical heterogeneity was quantified by the *Q*-Cochrane heterogeneity test (*Q* statistic with the degrees of freedom [*df*]) and the *I*² statistic.¹⁵ In the case of heterogeneity, the cause of heterogeneity was then explored in sensitivity analyses.

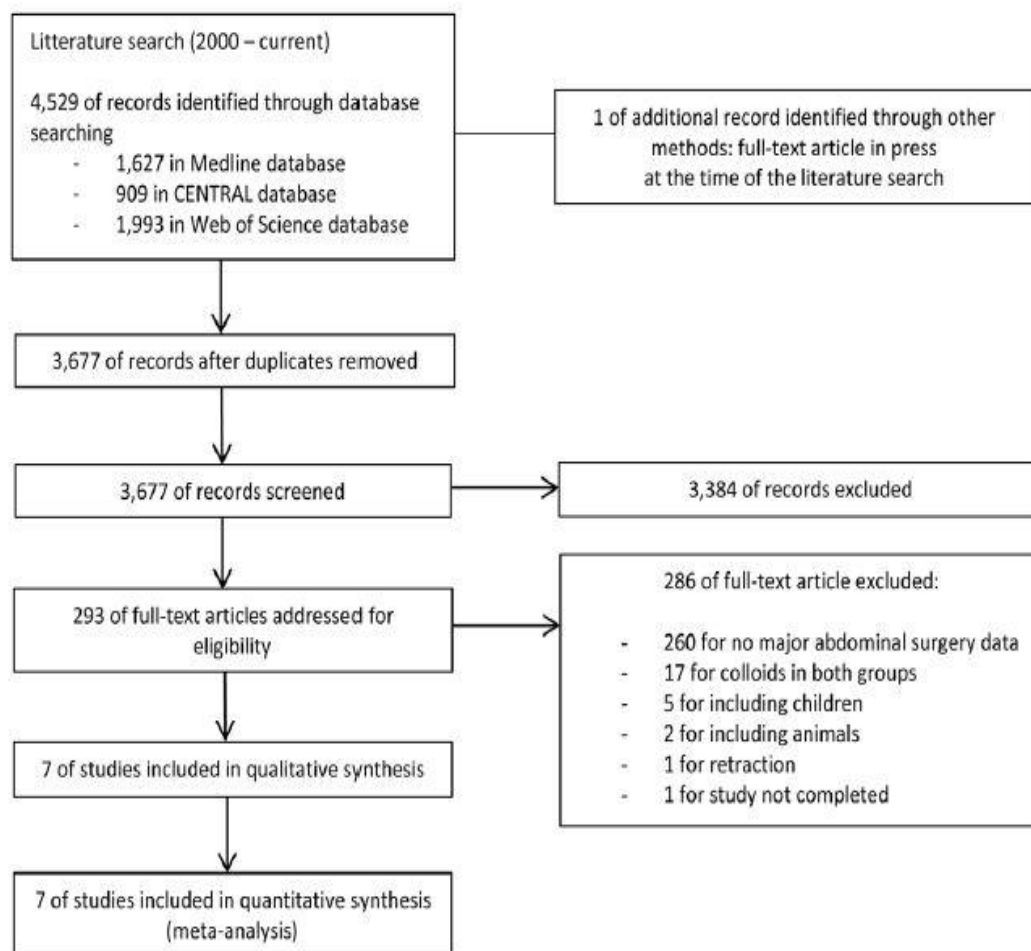


Figure 1. Flow chart for the study.

To explore more thoroughly the primary end point, we used TSA to assess the risk of random errors due to sparse data and multiple testing of accumulating data, and to calculate the required information size.²³ The calculated required information size²⁴ takes into account the control event proportion, the anticipated heterogeneity variance (D^2) of the meta-analysis, and the assumption of a plausible relative risk reduction (RRR) or relative risk increase (RRI).²⁴ We used an alpha risk of 5%,²⁵ a beta risk of 10%,²⁵ and a D^2 calculated according to the trials in the meta-analysis,^{23,24,26} or a D^2 of 20% if the measured heterogeneity was 0.26. As anticipated intervention effects for the primary outcome in the TSA, we used a realistic a priori RRI of 20% of the primary outcome (basal incidence rate assessed in the crystalloid group according to the data of the meta-analysis),^{23,26} as retrieved in recent large trials.^{3,12} We used an O'Brien-Fleming alpha and beta spending function and a variance-based O'Brien-Fleming heterogeneity correction.

When a statistical significance was found on a dichotomous outcome, we calculated the number needed to treat/to harm.²⁷ All tests were 2-sided. For the primary outcome, P value $<.05$ was considered statistically significant, and 95% CI were calculated.

For the 5 secondary outcomes, to adjust for multiple testing, we used the Bonferroni correction. P values $<.01$ were considered statistically significant, and 99% CI were calculated.²⁵

Table. Characteristics of Included Trials

Characteristics			Intervention group		Control group					
Study	Country (n)	Type of surgery	Subjects (n)	Type of fluid	Delivery method	Subjects (n)	Type of fluid	Delivery method	Maintenance fluid	Monitoring
Reismuseen et al (2014) ¹⁴	Denmark	Oysterectomy	17	6% HES (1.30/0.4)	200 mL boluses	16	Lactated Ringer's solution	200 mL boluses	Not stated	SV (esophageal Doppler)
Yates (2014) ²⁸	United Kingdom	Elective colorectal surgery	98	6% HES (1.30/0.4)	250 mL boluses	104	Lactated Ringer's solution	250 mL boluses	Lactated Ringer's solution	SV (pulse contour analysis)
Ghodazy (2017) ⁸	Iran	Open gastrointestinal surgery for resection and anastomosis	46	6% HES (1.30/0.4)	2 mL/kg/h	45	Lactated Ringer solution	6 mL/kg/h	Saline serum 1.5 mL/kg/h	Third space fluid loss calculated
Joosten et al (2018) ²⁹	Belgium	Open abdominal surgery >3 h scheduled	80	6% HES (1.30/0.4)	100 mL boluses	80	Plasmalyte	100 mL boluses	Plasmalyte 3 mL/kg/h	SV (closed loop system)
Cvetkovic (2018) ³⁰	Serbia	Major elective colorectal surgery for cancer	38	6% HES (1.30/0.4)	Not stated	42	Lactated Ringer's solution	Not stated	Not stated	SV (esophageal Doppler)
Kubon et al (2019) ¹	Austria	Moderate- to high-risk open and laparoscopically assisted abdominal surgery	534	6% HES (1.30/0.4)	250 mL boluses	523	Lactated Ringer's solution	250 mL boluses	Lactated Ringer's solution	SV (esophageal Doppler)
Futier et al (2020) ²	France	Abdominal surgery >2 h scheduled or not and/or high risk of postoperative complication	389	6% HES (1.30/0.4)	250 mL boluses	386	Saline serum 0.9%	250 mL boluses	Lactated Ringer's solution 4 mL/kg/h	SV (esophageal Doppler)

Abbreviations: HES, hydroxyethyl starch; SV, stroke volume.

RESULTS

Study Selection

We identified 4530 articles using the search strategy. We excluded 852 citations because of duplication and 3384 citations on the initial abstract screen because inclusion criteria were not met. After examination of the full text of the 293 selected papers, we included 7 RCTs for the systematic review and metaanalysis. 3,11,12,14,28–30 Figure 1 shows the study selection flowchart.

Study Description

The 7 studies^{3,11,12,14,28–30} involved a total of 2398 participants from 7 countries (Austria $n = 1$, Belgium $n = 1$, Denmark $n = 1$, France $n = 1$, Iran $n = 1$, Serbia $n = 1$, United Kingdom $n = 1$). Pooling all studies, 1197 participants were analyzed in the HES group and 1201 in the crystalloid group. The Table presents the characteristics of the studies included in the systematic review and meta-analysis.

Risk of Bias and Quality Assessment

All RCTs were identified with low to moderate risk of bias according to the Cochrane collaboration's tool. Supplemental Digital Content, Figures S1 and S2, <http://links.lww.com/AA/D717>, present the risk of bias assessment of included studies. Five studies^{3,11,12,14,29} were assessed having a low risk of bias and 2 studies^{29,30} having a moderate risk of bias. The primary outcome of 30-day AKI was reported in 6 studies. 3,11,12,28–30 Among the secondary end points, 30-day need for RRT was reported in 6 studies.^{3,11,12,14,28,30} Thirty-day mortality was reported in 4 studies.^{3,11,12,30} Intraoperative RBC transfusion was reported in 5 studies. 11,12,14,28,30 Intraoperative need for norepinephrine was reported in 5 studies.^{3,11,12,28,29} Thirty-day postoperative intra-abdominal complications was reported in 73,11,12,14,28–30 studies. The Table presents the characteristics of intravascular volume replacement for each study included. Only 6% HES 130/0.4 was used.

Primary Outcome: 30-Day AKI

Six studies^{3,11,12,28–30} including 2365 patients presented results for the 30-day AKI (Figure 2A: forest plot of 30-day AKI). The pooled RR across studies was 1.22 (95% CI, 0.94–1.59; $P = .13$), indicating no significant difference concerning the rate of 30-day AKI with the use of HES, when compared to crystalloid. There was low evidence of statistical heterogeneity for this outcome ($df = 5$, $P = .38$) with a corresponding I^2 statistic of 6%. In TSA (Supplemental Digital Content, Figure S3, <http://links.lww.com/AA/D717>), assuming a RRI of 20%, from an incidence of 30-day AKI of 8.9% in the crystalloid group to 10.7% in the HES group, neither the conventional boundaries nor the trial sequential monitoring boundaries for benefit, harm, or futility were crossed by Z curve. The required information size for 30-day AKI was estimated to be 12,351. The accrued information size was 2365. The TSA analysis results suggest that there is not nearly enough evidence in the existing meta-analyses on this research question to make a definitive conclusion. More research is needed.

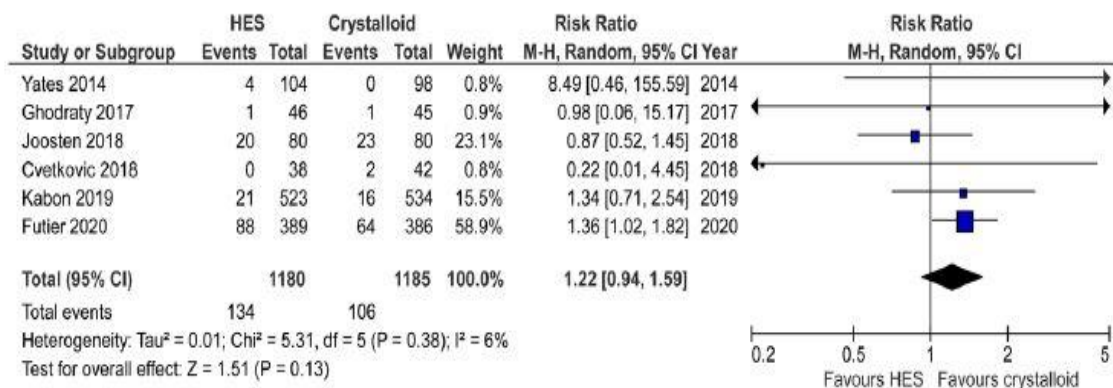


Figure 2. Forest plot of 30-d acute kidney injury. CI indicates confidence interval; df, degrees of freedom; HES, hydroxyethyl starch; I², heterogeneity statistic; M-H, Mantel-Haenszel.

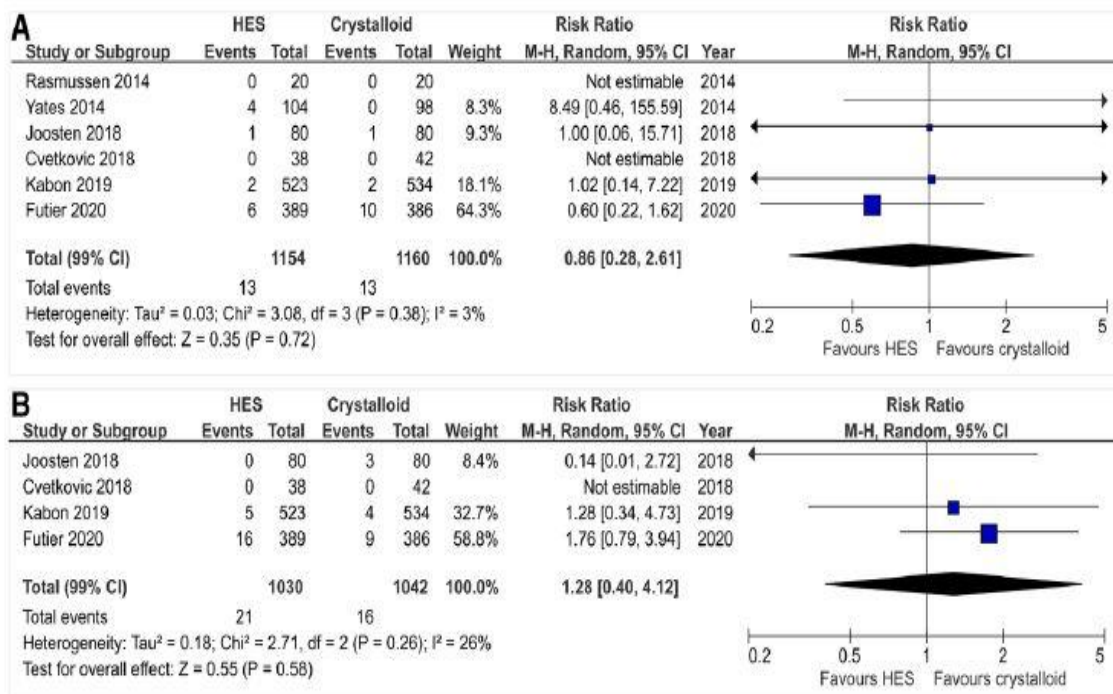


Figure 3. Forest plots of 30-d need for RRT and 30-d mortality. A, Forest plot of 30-d need for RRT. B, Forest plot of 30-d mortality. To adjust for multiple testing, we reported 99% CI after Bonferroni correction. CI indicates confidence interval; df, degrees of freedom; HES, hydroxyethyl starch; I², heterogeneity statistic; M-H, Mantel-Haenszel; RRT, renal replacement therapy.

Secondary Outcomes

Need for Renal Replacement Therapy.

Six studies^{3,11,12,14,28,30} including 2314 patients reported data on 30-day need for RRT (Figure 3A: forest plot of 30-day need for RRT). The pooled RR across studies was 0.86 (99% CI, 0.28–2.61; $P = .72$), indicating no significant difference concerning the rate of 30-day need for RRT with the use of HES, when compared to crystalloid. There was low evidence of statistical heterogeneity for this outcome ($df = 3$, $P = .38$), with a corresponding I^2 statistic of 3%. 30-Day Mortality. Four studies^{3,11,12,30} including 2072 patients reported rate of mortality (Figure 3B: forest plot of 30-day mortality). The pooled RR across studies

was 1.28 (99% CI, 0.40–4.12; $P = .58$), indicating no significant difference in 30-day mortality with HES when compared to crystalloid. There was low evidence of statistical heterogeneity for this outcome ($df = 2$; $P = .26$) and a corresponding I^2 statistic of 26%.

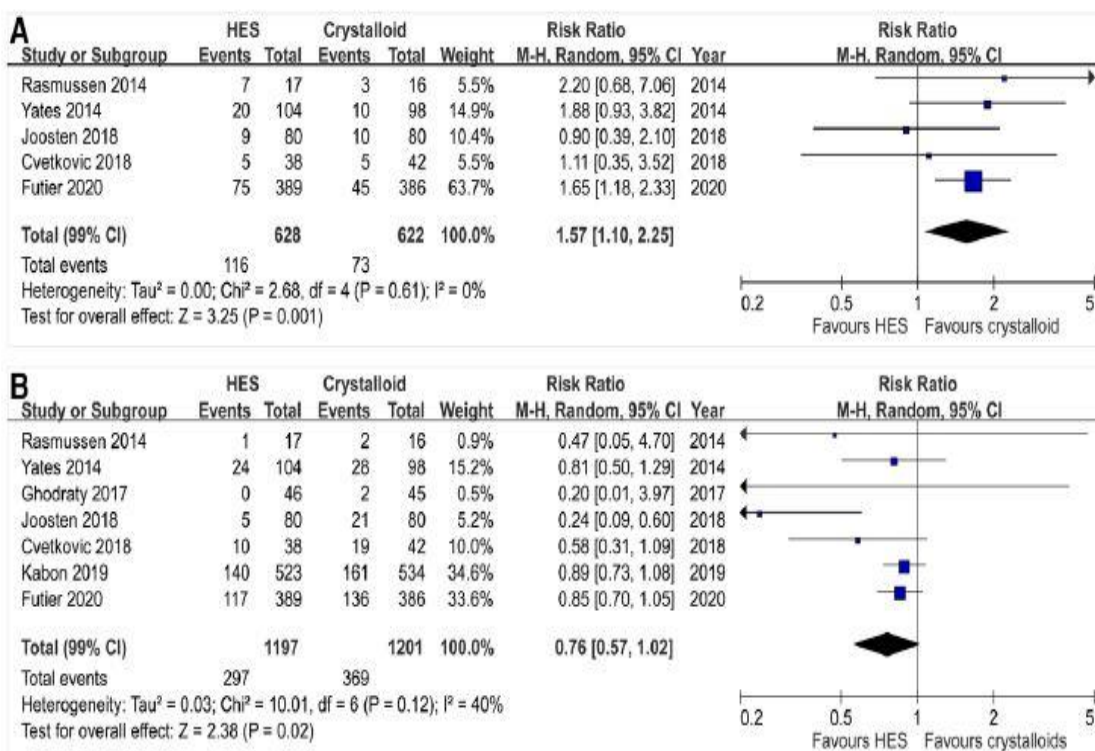


Figure 4. Forest plots of intraoperative RBC transfusion and 30-d postoperative intra-abdominal complications. A, Forest plot of intraoperative RBC transfusion. B, Forest plot of 30-d postoperative intra-abdominal complications. To adjust for multiple testing, we reported 99% confidence intervals after Bonferroni correction. CI indicates confidence interval; df , degrees of freedom; HES, hydroxyethyl starch; I^2 , heterogeneity statistic; M-H, Mantel-Haenszel; RBC, red blood cell.

Blood Loss.

Five studies^{11,12,14,28,30} including 1250 patients reported results for the incidence of RBC transfusion (Figure 4A: forest plot of intraoperative RBC transfusion). The pooled RR across studies was 1.57 (99% CI, 1.10–2.25; $P = .001$), indicating a higher rate of intraoperative RBC transfusion associated with the use of HES when compared to crystalloid. There was low evidence of statistical heterogeneity for this outcome ($df = 4$, $P = .61$), with a corresponding I^2 statistic of 0%. The number needed to harm was 15 (99% CI, 6.8–85).

Five studies^{3,11,12,28,29} including 2285 patients reported results for the intraoperative need for norepinephrine (Supplemental Digital Content, Figure S4, <http://links.lww.com/AA/D717>: forest plot of intraoperative need for norepinephrine). The pooled RR across studies was 0.53 (99% CI, 0.13–2.23; $P = .26$), indicating no significant difference for the intraoperative need for norepinephrine associated with the use of HES when compared to crystalloid. There was a substantial heterogeneity for this outcome ($df = 1$, $P = .002$), with a corresponding I^2 statistic of 90%.

Postoperative Intra-abdominal Complications.

Seven studies^{3,11,12,14,28–30} including 2398 patients presented results for 30-day postoperative intra-abdominal complications (Figure 4B: forest plot of 30-day postoperative intra-abdominal complications). The pooled RR across studies was 0.76 (99% CI, 0.57–1.02; $P = .02$) indicating no significant difference after Bonferroni correction of 30-day postoperative intraabdominal complications with HES when compared to crystalloids. There was a moderate heterogeneity for this outcome ($df = 6$, $P = .12$) with a corresponding I^2 statistic of 40%. Within postoperative complications, the observed treatment effect appeared to be consistent across anastomotic leakage, reoperation, and surgical site infection but this was not tested (Supplemental Digital Content, Figures S5–S7, <http://links.lww.com/AA/D717>).

DISCUSSION

This systematic review, meta-analysis, and TSA of 7 RCTs^{3,11,12,14,28–30} suggested that a HES intravascular volume replacement strategy in patients undergoing major abdominal surgery does not increase the risk of 30-day AKI when compared to a crystalloid intravascular volume replacement strategy. However, the 95% CI of the RR (0.94–1.59) for 30-day AKI highlights the potential for HES to increase the risk of AKI by 60%. This would be clinically important and so the results cannot be accurately interpreted as reliably consistent with “no effect.”

Using HES might be associated with higher rates of intraoperative RBC transfusion (Figure 4A), even if no conclusion can be drawn from the analysis of secondary outcomes and no statistical difference in the need for norepinephrine was found (Supplemental Digital Content, Figure S4, <http://links.lww.com/AA/D717>).

Our findings are largely consistent with the many RCTs^{8,18} and meta-analyses^{31–38} performed in the critically ill population, with results suggesting higher rates of RBC transfusion associated with the use of HES. Contrary to our results in the field of major abdominal surgery, meta-analyses in the field of critical care have also found an increased risk of need for RRT and mortality.^{32,33}

One must keep in mind that the population of patients undergoing major abdominal surgery differs widely from the population of critically ill patients. In the 7 studies included for analysis, the patients were mostly noncritically ill patients undergoing scheduled procedures. Indeed, only the study by Futier et al¹² included patients undergoing unscheduled surgery (13 of 775 patients) and patients with American Society of Anesthesiologists (ASA) physical status of IV (11 of 775 patients). Only 2 studies^{11,12} reported more than 5% of AKI. In our meta-analysis, <1% of overall patients needed RRT, and <2% of overall patients died. Thus, neither any of the recent big RCTs performed in abdominal surgery^{3,11,12} nor our meta-analysis were powered to detect differences in AKI, RRT, or mortality. According to the TSA performed for the primary outcome (Figure 2B), 12,351 randomized patients would be needed to bring out a 20% RRI, from 8.9% to 10.7% of 30-day AKI with a high-level of certainty. Another difference between patients undergoing major abdominal surgery and critically ill patients lies in the prominence of surgical concerns.³⁹ Renal prognosis may be altered by postoperative surgical complications and the need for reoperation, extended antibiotic treatment, or intensive care unit stay.⁴⁰

One of the strengths of the present systematic review and meta-analysis is the large sample size and the low statistical heterogeneity. Second, it is to our knowledge the first meta-analysis to focus on 1 type of colloid (third-generation HES, 6% HES 130/0,4) in 1 category of surgery (major abdominal surgery). This limits the discrepancies between studies and strengthens the external validity of our results, and explains why studies before 2000 were not included. Our systematic review with meta-analysis has limitations. First, if protocols for fluid management are similar, discrepancies do appear in the stroke volume and mean arterial pressure objectives, and in the protocol for use of norepinephrine. Both elements play an important role in perioperative fluid management.⁴¹ Second, due to the low number of studies in the review, the presence of publication bias by funnel plots could not be assessed,⁴² and the results are highly dependent on the quality of included trials, with some outcomes and variables being not comparable. Some interesting outcomes as postoperative transfusion could not be analyzed.

The clinical heterogeneity would have been too wide between studies. No postoperative transfusion strategy was defined in trials. Indeed, patients underwent different surgeries with different postoperative managements, and potentially different transfusion thresholds. Third, the TSA highlighted a lack of power to detect a statistical difference between groups for the main outcome. Fourth, normal saline may be harmful on renal function and outcomes in critically ill patients when compared to the use of balanced crystalloid solutions.⁴³ It is worth noting that 2 studies used normal saline (Table), the study by Futier et al¹² used boluses of saline serum in the control group while using lactated Ringer's solution for maintenance fluid, and the study by Ghodratty et al²⁹ used serum saline for maintenance fluid while using lactated Ringer's solution for boluses in the control group. However, each study but one²⁹ used a protocol with stroke volume monitoring to guide fluid infusion, and each study respected a maximal amount of infused HES of 33 mL/kg/d.⁴⁴ Finally, the results on the main outcome and need for RRT and 30-day mortality show wide 95% CI (Figures 2 and 3). Those CIs include values indicating potential substantial harm in the HES group for those outcomes.

To conclude, this systematic review with metaanalysis suggests that HES intravascular volume replacement was not associated with a higher risk of 30-day AKI when compared to crystalloid intravascular volume replacement, without reaching a sample size sufficient to conclude to the lack of difference with certainty. CI and TSA do not exclude harmful effects of HES intravascular volume replacement on the renal function. Using HES for intravascular volume replacement in patients undergoing major abdominal surgery might be associated with higher intraoperative RBC transfusion. This study brings out that applying critical care data appears to be exerting caution in the surgical population, especially in major abdominal surgery. Further data from large multicenter studies or big data banks including thousands of patients with major abdominal surgery are needed to draw firm conclusions regarding the association of HES and AKI, RBC transfusion or intra-abdominal complications.

DISCLOSURES

Name:

Joris Pensier, MD.

Contribution:

This author helped with conception and design of the study, acquisition of the data, analysis of the data, drafting the submitted article, and final approval of the version to be published.

Conflicts of Interest:

None.

Name:

Lucas Deffontis, MD.

Contribution:

This author helped with conception and design of the study, acquisition of the data,

Funding:

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Conflicts of Interest:

See Disclosures at the end of the article. analysis of the data, drafting the submitted article, and final approval of the version to be published.

Conflicts of Interest:

None.

Name:

Amélie Rollé, MD.

Contribution:

This author helped with analysis of the data, drafting the submitted article, and final approval of the version to be published.

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Name:

Yassir Aarab, MD.

Contribution:

This author helped with analysis of the data, drafting the submitted article, and final approval of the version to be published.

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Name:

Mathieu Capdevila, MD.

Contribution:

This author helped with analysis of the data, drafting the submitted article, and final approval of the version to be published.

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Name:

Clément Monet, MD.

Contribution:

This author helped with analysis of the data, drafting the submitted article, and final approval of the version to be published.

Conflicts of Interest:

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Name:

Julie Carr, MD.

Contribution:

This author helped with analysis of the data, drafting the submitted article, and final approval of the version to be published.

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Name:

Emmanuel Futier, MD, PhD.

Contribution:

This author helped to the conception and design of the study, to the analysis and interpretation of data, to drafting the submitted article, and to provide final approval of the version to be published.

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Name:

Nicolas Molinari, PhD.

Contribution:

This author helped with analysis of the data, drafting the submitted article, and final approval of the version to be published.

Conflicts of Interest:

None.

Name:

Samir Jaber, MD, PhD.

Contribution:

This author helped with conception and design of the study, analysis and interpretation of data, drafting the submitted article, and final approval of the version to be published.

Conflicts of Interest:

S. Jaber reports receiving consulting fees from Drager, Medtronic, Fresenius, Baxter, and Fisher & Paykel.

Name:

Audrey De Jong, MD, PhD.

Contribution:

This author helped with conception and design of the study, analysis and interpretation of data, drafting the submitted article, and final approval of the version to be published.

Conflicts of Interest:

None.

This manuscript was handled by:

Alexander Zarbock, MD.

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