Association of Hydroxyethyl Starch Administration With Mortality and Acute Kidney Injury in Critically Ill Patients Requiring Volume Resuscitation

A Systematic Review and Meta-analysis

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Importance Hydroxyethyl starch is commonly used for volume resuscitation yet has been associated with serious adverse events, including acute kidney injury and death. Clinical trials of hydroxyethyl starch are conflicting. Moreover, multiple trials from one investigator have been retracted because of scientific misconduct.

Objectives To evaluate the association of hydroxyethyl starch use with mortality and acute kidney injury.

Data Sources Randomized controlled trials from MEDLINE, EMBASE, CENTRAL, Global Health, HealthStar, Scopus, Web of Science, the International Clinical Trials Registry Platform (inception to October 2012), reference lists of relevant articles, and gray literature.

Study Selection Two reviewers independently identified randomized controlled trials comparing hydroxyethyl starch with other resuscitation fluids in critically ill patients receiving acute volume resuscitation.

Data Extraction Two reviewers independently extracted trial-level data including population characteristics, interventions, outcomes, and funding sources. Risk of bias was assessed using the risk of bias tool; the strength of evidence was adjudicated using the GRADE methodology.

Results We included 38 eligible trials comparing hydroxyethyl starch to crystalloids, albumin, or gelatin. The majority of trials were categorized as having an unclear risk or high risk of bias. For the 10 880 patients in studies contributing mortality data, the risk ratio (RR) for death among patients randomized to receive hydroxyethyl starch was 1.07 (95% CI, 1.00 to 1.14; I^2, 0%; absolute risk [AR], 1.20%; 95% CI, −0.26% to 2.66%). This summary effect measure included results from 7 trials performed by an investigator whose subsequent research had been retracted because of scientific misconduct. When we excluded these 7 trials that involved 590 patients, hydroxyethyl starch was found to be associated with increased mortality among 10 290 patients (RR, 1.09; 95% CI, 1.02 to 1.17; I^2, 0%; AR, 1.51%; 95% CI, 0.02% to 3.00%), increased renal failure among 8725 patients (RR, 1.27; 95% CI, 1.09 to 1.47; I^2, 26%; AR, 5.45%; 95% CI, 0.44% to 10.47%), and increased use of renal replacement therapy among 9258 patients (RR, 1.32; 95% CI, 1.15 to 1.50; I^2, 0%; AR, 3.12%; 95% CI, 0.47% to 5.78%).

Conclusion and Relevance In critically ill patients requiring acute volume resuscitation, use of hydroxyethyl starch compared with other resuscitation solutions was not associated with a decrease in mortality. Moreover, after exclusion of 7 trials performed by an investigator whose research has been retracted because of scientific misconduct, hydroxyethyl starch was associated with a significant increased risk of mortality and acute kidney injury. Clinical use of hydroxyethyl starch for acute volume resuscitation is not warranted due to serious safety concerns.

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FLUIDS ARE A CORE ELEMENT IN the resuscitation of critically ill patients and the relative superiority and safety of different resuscitation solutions has been the focus of considerable debate. Crystalloid solutions are inexpensive and readily available, while colloid solutions may minimize resuscitation volumes, and may sustain intravascular volume for longer durations.[1] Conflicting results from clinical trials and systematic reviews have not resolved this debate, leaving clinicians to select resuscitation fluids based on suboptimal evidence.

Hydroxyethyl starch is a synthetic colloid derived from partially hydrolyzed and variably hydroxyethylated plant starch, and is commonly administered to patients requiring fluid resuscitation.[2] Clinical trials and systematic reviews have suggested a greater incidence of renal damage and mortality in patients receiving hydroxyethyl starch,[3-6] but these findings have been inconsistent.[7,8] The differing results may be due to a combination of factors including differing patient populations,

For editorial comment see p 723.

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types and volumes of hydroxyethyl starch and the safety profile of the comparator fluids.[9] A further explanatory factor may be the influence of research misconduct or author bias.[10,11]

In 2011, 86% (88 of 102) of the research published by Joachim Boldt, MD, since 1999 was retracted after a government investigation reported research misconduct reflecting failure to acquire ethical approval for research and fabrication of study data.[10,11] The effect of these retractions has been far-reaching. All major systematic reviews and clinical guidelines are now being revised to account for the retracted data and permit sensitivity analyses on the remaining publications by Boldt et al.

We performed a quantitative systematic review of randomized controlled trials comparing hydroxyethyl starch with other intravenous fluids for acute fluid resuscitation in critically ill patients. Our primary outcomes of interest were mortality and the incidence of acute kidney injury. Additionally, we investigated the influence of the studies conducted by Boldt and his colleagues on these outcomes.

METHODS

Using an a priori published protocol,[12] we conducted our systematic review using methodological approaches outlined in the *Cochrane Handbook for Systematic Reviewers*[13] and reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) criteria.[14] A technical panel of experts from multiple fields (eg, hematology, internal medicine, critical care medicine, research methodology) formulated the review questions, reviewed the search strategies and review methods, and provided input throughout the review process.

Populations, Interventions, Comparators, Outcome Measures, Settings, and Study Designs

We included only randomized, controlled trials of critically ill adult patients treated in an emergency or intensive care setting (eTable 1 available at http://www.jama.com). The primary research question was "In critically ill patients requiring acute volume resuscitation, what is the comparative efficacy and potential harm of hydroxyethyl starch solutions compared with other resuscitation fluids?"

The main outcome measures were mortality and renal injury according to the RIFLE criteria[15] stratifying kidney damage into: Risk of renal dysfunction, Injury to the kidney, Failure of kidney function, Loss of kidney function, and End-stage kidney disease. Secondary outcomes were the incidence of renal recovery (10% of baseline function or independence of renal replacement therapy), incidence of major bleeding, transfusion of red blood cells, and reported allergic reactions. We also evaluated intensive care unit and overall length of stay, as well as the duration of mechanical ventilation. Inclusion and exclusion criteria are presented in eTable 2.

Search Strategy for Identification of Studies

We searched MEDLINE, EMBASE, CENTRAL (Cochrane Library), Global Health, and HealthStar from inception to October 2012 for relevant citations of published trials using individualized search strategies prepared for each database. The MEDLINE strategy is presented in eTable 3. We searched the World Health Organization's International Clinical Trials Registry Platform and hand-searched relevant conference proceedings for the preceding 5 years to identify planned, ongoing, or recently completed but unpublished trials of starch-based solutions (eTable 4). We performed forward searches in Scopus and Web of Science to identify additional citations that might have been missed through traditional searching methods. Finally, the reference lists of narrative and systematic reviews and included trials were hand-searched for relevant citations. We performed reference management in EndNote (version X5, Thomson Reuters).

Study Selection

We used a 2-stage process for study screening and selection using standardized and piloted screening forms. Two reviewers independently screened the titles and abstracts of search results to determine whether a citation met the inclusion criteria. The full text of citations classified as *include* or *unclear* were reviewed independently with reference to the predetermined inclusion and exclusion criteria. Discrepancies between the 2 reviewers were resolved through consensus by discussion with a third reviewer, as required.

Data Abstraction and Management

Two reviewers independently extracted data, using standardized and piloted data extraction forms, from included trial reports. Discrepancies between the 2 reviewers were resolved through consensus in discussion with a third reviewer, as required. Extracted data included demographics of the enrolled patient population, interventions, study outcomes, and funding sources. Data management was performed using Microsoft Excel 2010 (Excel version 14, Microsoft Corp).

Assessment of Methodological Quality and Potential Risk of Bias

We assessed internal validity using the Cochrane Collaboration's Risk of Bias tool.[16] This tool consists of 6 domains and assesses 5 specific biases. We also assessed the source(s) of funding for each study and its potential influence on the outcome measures. We used information pertaining to methodological quality and risk of bias to guide sensitivity analyses and to explore sources of heterogeneity. To investigate the effect of trials conducted by Boldt, we performed a sensitivity analysis by author teams (Boldt et al vs other author teams).

Measures of Treatment Effect

We analyzed data from the included studies using Review Manager (RevMan, version 5.2, the Nordic Cochrane Center, the Cochrane Collaboration), Comprehensive Meta-Analysis

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(Biostat Inc, version 2.0), and Microsoft Excel (Excel version 14, Microsoft Corp). A formal meta-analysis was conducted if the data were statistically and clinically homogeneous. We expressed pooled continuous effect measures as the mean difference or standardized mean difference with 95% CIs. Pooled dichotomous data were expressed as risk ratio (RR), or Peto odds ratio (OR) in the event of rare outcomes[17] and absolute risk (AR). We used the random-effects model for all analyses, with the exception of the Peto OR (fixed effect model).

Statistical heterogeneity of the data was explored and quantified, using the I^2 test, with 95% uncertainty intervals.[18] If significant statistical heterogeneity was detected (I^2>50%), a sensitivity analysis was conducted. Publication bias was assessed using funnel plot techniques, the Begg rank test, and the Egger regression test, as appropriate given the known limitations of these methods.[19] All tests of statistical inference reflect a 2-sided α of .05.

Subgroup, Sensitivity, and Meta-Regression Analyses

Subgroup, sensitivity, and meta-regression analyses were performed to determine summary effect estimates of hydroxyethyl starch in specific patient populations, effects relative to specific comparator fluids, and the effect of other potentially confounding factors.[12] Analyses were dependent on the number of studies included and the availability of appropriate outcomes and covariates. In additional analyses, trials conducted by Boldt et al were excluded.

Grading the Evidence

We graded the strength of evidence for our primary outcomes (external validity) using the GRADE methodology.[20] Two reviewers evaluated the strength of the body of evidence. GRADE methodology assesses the evidence according to the following domains: study design, risk of bias, inconsistency, indirectness, imprecision, and other considerations (eg, evidence of publication bias). This approach classifies the strength of evidence as *high*, *moderate*, *low*, or *very low*.

RESULTS

Of the 3779 citations identified from electronic and hand-searches, we included 38 unique trials (plus 4 companion publications) with 12 to 7000 patients (median, 42; interquartile range [IQR], 28 to 122) (TABLE 1, TABLE 2, TABLE 3, and FIGURE 1). Trials were published between 1982 and 2012 (median, 2004; IQR, 1996 to 2010), and all but one[21] were published in peer-reviewed journals. Most trials were single-center randomized trials of patients with sepsis, trauma, or both in an acute care setting in European centers and published in an English language journal. Four[22-24] trials were from North America, and five[25-28] were published in non-English languages (eTable 5 available at http://www.jama.com).

The mean age of study patients ranged from 28 to 79 years; 61% of patients were men and 95% of the trials were adjudicated to be of unclear risk or high risk of bias; 3 trials[29,30,54] were considered to have a low risk of bias (eTable 6).

Primary Outcomes

Mortality. For 10 880 patients involved in the 35 studies contributing mortality data, the pooled RR for death among patients randomized to receive hydroxyethyl starch was 1.07 (95% CI, 1.00 to 1.14; I^2, 0%; AR, 1.20%; 95% CI, −0.26% to 2.66%) (FIGURE 2). We did not detect publication bias, but given that the majority of trials were considered to be of unclear or high risk of bias, we graded the overall strength of evidence as low.

In 7 trial reports by Boldt et al[7,29-34] that had not been retracted (investigations into research misconduct and ethics violations were limited to trials published since 1999; the 7 trials included herein were published before 1999), we observed no association between hydroxyethyl starch and all-cause mortality among the studies' 590 patients (RR, 0.91; 95% CI, 0.74 to 1.12; I^2, 0%; AR, −5.26%; 95% CI, −12.08% to 1.56%). In contradistinction to the findings of Boldt et al, pooled results from 10 290 patients involved in 28 trials conducted by other investigators demonstrated that hydroxyethyl starch was significantly associated with increased death (RR, 1.09; 95% CI, 1.02 to 1.17; I^2, 0%; AR, 1.51%; 95% CI, 0.02% to 3.00%). The heterogeneity between the 2 groups of trials was substantially high[55] (I^2, 59.4%). After removing the 7 trials from the analyses of mortality, none of the other mortality subgroups, sensitivity analyses, or meta-regression analyses had marked statistical heterogeneity between the trials (eTable 7). Given the measured statistical heterogeneity, coupled with the history of retractions of other trials conducted by Boldt et al, we excluded these 7 trials from further analyses. Without these trials, we graded the overall strength of evidence as moderate.

Acute Kidney Injury

Ten trials* reported on the incidence of renal replacement therapy use in 9258 patients (FIGURE 3). Pooled results demonstrate a significant relationship between hydroxyethyl starch administration and risk of receiving renal replacement therapy (RR, 1.32; 95% CI, 1.15 to 1.50; I^2, 0%; AR, 3.12%; 95% CI, 0.47% to 5.78%) compared with other fluids (Figure 3). Two trials[52,53] involving 996 patients reported all the RIFLE criteria for acute kidney injury, whereas another 5 trials[3,4,35,44,54] reported on individual RIFLE components in 7886 patients (TABLE 4). The incidence of acute renal failure reported in a total of 5 trials[3,44,52,54] involving 8725 patients was significantly higher in receiving hydroxyethyl starch (RR, 1.27; 95% CI, 1.09 to 1.47; I^2, 26%; AR, 5.45%; 95% CI, 0.44% to 10.47%). We did not detect evidence of publication bias for this outcome and graded the strength of evidence as moderate.

Secondary Outcome Measures

Among 6909 patients involved in 10 trials,† hydroxyethyl starch adminis-

*References 3, 4, 22, 26, 35, 37, 44, 52-54.
†References 4, 24, 25, 35-37, 42, 47, 54, 56.

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tration was associated with a reduction in urine output (standardized mean difference, −0.15; 95% CI, −0.19 to −0.10; I^2, 0%) (Table 4). Included trials did not report changes in the glomerular filtration rates, incidence of renal recovery, or the incidence of anuria among patients. No differences in intensive care unit length of stay[21,40,46,52,54] (n=7016, 5 trials) or overall hospital length of stay[21,23,26,35,52,54] (n=7337, 6 trials) were reported. There was no reported difference in the average duration of ventilation days[32,35-54] (n=6984, 3 trials). The reports on the incidence

Table 1. Characteristics of Individual Trials, Patient Populations, and Interventions, 1988-1998

					Intervention		Control	
Source	Population	Overall Age, Mean (SD), y[a]	Severity of Illness, Mean (SD)	Trigger for Fluids	Protocol	No. of Patients	Protocol	No. of Patients
Haupt and Rachow,[24] 1982	Hypovolemic shock	77 (10)	NR	PCWP <10 mm Hg	6% HES 450/0.7, 250 mL boluses	9	5% ALB (n = 9); 0.9% NaCl (n = 8), 250 mL boluses	17
Falk et al,[56] 1988	Septic shock	Median, 78	NR	PCWP <15 mm Hg	6% HES 450/0.7, 250 mL boluses	6	5% ALB, 250 mL boluses	6
Rackow et al,[50] 1989	Severe sepsis	69 (13)	NR	PCWP <15 mm Hg	10% HES 200-300/0.4-0.5, 250 mL boluses, maximum 2000 mL	10	5% ALB 250 mL boluses, maximum 2000 mL	10
Randell et al,[57] 1990	Organ donors	35 (12)	NR	CVP <5 mm Hg	6% HES 120/0.7, 500 mL-1500 mL	9	RL or 0.45% NaCl, as needed	7
Nagy et al,[23] 1993	Trauma	NR	ISS: 18 (10)	U/O <30 mL/h, SBP <100 mm Hg	10% HES 200-300/0.4-0.5, maximum 4000 mL	21	RL as needed	20
Beards et al,[49] 1994	Hypovolemia	55	NR	U/O <15 mL/h, MAP <80 mm Hg, or PCWP <10 mm Hg	6% HES 450/0.7, 500 mL bolus	13	4% GEL, 500 mL bolus	15
Berard et al,[26] 1995	GI bleeding	60 (16)	NR	NR	HES	146	GEL	153
Boldt et al,[31] 1995	Sepsis/trauma	48	APACHE: 20 (3)	CVP/PCWP <12 mm Hg	10% HES 200/0.5, as needed	30	20% ALB, as needed	30
Boldt et al,[32] 1996	Sepsis/trauma	51	APACHE: 19 (3)	PCWP <10 mm Hg	10% HES 200/0.5, as needed	28	20% ALB, as needed	28
Boldt et al,[33] 1996	Sepsis/trauma	47 (12)	APACHE: 20 (3)	CVP/PCWP <12 mm Hg	10% HES 200/0.5, as needed	28	20% ALB, as needed	28
Boldt et al,[29] 1996	Sepsis/trauma	49 (12)	APACHE: 19 (3)	PCWP <12 mm Hg	10% HES 200/0.5, as needed	30	20% ALB, as needed	30
Boldt et al,[30] 1996	Trauma	37 (13)	APACHE: 20 (3)	CVP/PCWP <12 mm Hg	10% HES 200/0.5, as needed	15	20% ALB, as needed	15
Boldt et al,[34] 1996	Sepsis	57 (11)	APACHE: 24 (3)	CVP/PCWP <10 mm Hg	10% HES 200/0.5, as needed	14	20% ALB, as needed	14
Boldt et al,[7] 1998	Sepsis/trauma	48 (11)	APACHE: 21 (3)	PCWP <12 mm Hg	10% HES 200/0.5 as needed	150	20% ALB as needed	150
Younes et al,[48] 1998	Trauma	33 (12)	RTS: 9 (3)	SBP <100 mm Hg	10% HES 200-300/0.4-0.5, 250 mL boluses	12	0.9% NaCl, 250 mL boluses	11

Abbreviations: ABL, albumin; APACHE, Acute Physiology and Chronic Health Evaluation II; CVP, central venous pressure; GEL, gelatin; GI, gastrointestinal; HES, hydroxyethyl starch; Hg, mercury; ISS, Injury Severity Score; MAP, mean arterial pressure; NaCl, sodium chloride; NR, not reported; PCWP, pulmonary capillary wedge pressure; RL, Ringer's lactate; RTS, revised trauma score; SBP, systolic blood pressure; U/O, urine output.

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Table 2. Characteristics of Individual Trials, Patient Populations, and Interventions, 2000-2009

Source	Population	Overall Age, Mean (SD), y[a]	Severity of Illness, Mean (SD)	Trigger for Fluids	Intervention		Control	
					Protocol	No. of Patients	Protocol	No. of Patients
Asfar et al,[47] 2000	Sepsis	65 (14)	SAPS: 49 (22)	SBP >90 mm Hg or PCWP <12 mm Hg	6% HES 200/0.6, 500 mL bolus	16	4% GEL, 500 mL bolus	18
Carli et al,[51] 2000	Trauma	39 (18)	RTS 6 (2)	SBP <100 mm Hg	6% HES 200/0.5, maximum 2000 mL	85	GEL, maximum 2000 mL	79
Schortgen et al,[3] 2001	Severe sepsis/ septic shock	HES median, 69 (IQR, 47-74) GEL median, 56 (IQR, 44-71)	SAPS median (IQR): HES: 53 (38-67) GEL: 50 (42-64)	Deemed by the physician to require fluid loading	6% HES 200/0.6-0.66, 500 mL (maximum 33 mL/kg the first d, then 20 mL/kg/d) (April 1998-April 1999); Maximum 4 d HES of 80 mL/kg (April 1999-Sep 1999)	65	3% GEL, as needed	64
Veneman et al,[45] 2004	Sepsis/SIRS	69	APACHE: 22 (7)	MAP <70 mm Hg, CVP <5 mm Hg	10% HES 200/0.43-0.55, 500-1000 mL/d for 72 h	30	20% ALB (n = 15), 300 mL/d for 72 h; 0.9% NaCl (n = 16), 1000 mL/d for 72 h	31
Molnar et al,[46] 2004	Sepsis	53 (16)	SAPS: 34 (18)	ITBVI <900 mL/m^2	6% HES 200/0.6, 250 mL bolus, maximum 1000 mL	15	4% GEL, 250 mL bolus, maximum 1000 mL	15
Chen et al,[25] 2006	Burns	37 (14)		NR	HES 130/0.4, 60 g/L (1/4 over 3 h; 1/2 over next 8 h)	33	Plasma, 1.5 mL/kg (1/4 over 3h; 1/2 over next 8 h)	33
Li et al,[43] 2008	Septic shock	45 (24)	APACHE: 10 (4)	NR	HES, 300-500 mL	44	4% NaCl, 300-1000 mL	47
McIntyre et al,[22] 2008	Sepsis	63 (15)	APACHE: 21 (6)	SBP <90 mm Hg, MAP <65 mm Hg	10% HES 200-300/0.4-0.5, 500 mL bolus, maximum 3000 mL	21	0.9% NaCl, 500 mL bolus, maximum 3000 mL	19
Brunkhorst et al,[44] 2008	Septic shock	65 (14)	APACHE: 20 (7)	CVP <8 mm Hg, MAP <70 mm Hg	10% HES 200/0.45-0.55, Maximum 20 mL/kg/d	297	RL	303
van der Heijden et al,[42] 2009	Septic and nonseptic ICU patients	57 (15)	APACHE: 12 (5)	Pressure limits, CVP	6% HES 200/0.45-0.55, 200 mL boluses, maximum 1800 mL	12	0.9% NaCl (n = 12), 4% GEL (n = 12), 5% ALB (n = 12), 200 mL bolus, maximum 1800 mL	36
Dolecek et al,[41] 2009	Severe sepsis	HES median, 47 (range, 19-81) GEL median, 43 (range, 23-67)	SOFA: 8 (3)	ITBVI < 850 mL/m^2, or CI <3.5 L/min/m^2	6% HES 130/0.4, 250 mL every 6 h	26	20% ALB, 100 mL every 12 h	30

Abbreviations: ABL, albumin; APACHE, Acute Physiology and Chronic Health Evaluation II; CVP, central venous pressure; GEL, gelatin; HES, hydroxyethyl starch; Hg, mercury; ICU, intensive care unit; IQR, interquartile range; ITBVI, intrathoracic blood volume index; MAP, mean arterial pressure; NaCl, sodium chloride; NR, not reported; RL, Ringer's lactate; RTS, revised trauma score; RV, respiratory variation; SAPS, Simplified Acute Physiology Score II; SBP, systolic blood pressure; SIRS, systematic inflammatory response syndrome; U/O, urine output.

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Table 3. Characteristics of Individual Trials, Patient Populations, and Interventions, 2010-2012

Source	Population	Overall Age, Mean (SD), y[a]	Severity of Illness, Mean (SD)	Trigger for Fluids	Intervention		Control	
					Protocol	No. of Patients	Protocol	No. of Patients
Dubin et al,[36] 2010	Severe sepsis	64 (16)	SOFA: 9 (3)	CVP <8 mm Hg, MAP ≤ 65 mm Hg	6% HES 130/0.4, as needed	12	0.9% NaCl, as needed	13
Gondos et al,[38] 2010	Postoperative hypovolemia	58 (15)	APACHE median (range): HES: 14 (8-21) GEL: 15 (8-23) ALB: 11 (7-19) RL: 15 (8-22)	Signs of hypovolemia and GEDVI <600 mL/m^2 or SVV >10%	6% HES 130/0.4 10 mL/kg	50	4% GEL (n = 50); 5% ALB (n = 50); RL (n = 50); 10 mL/kg	150
Heradstveit et al,[39] 2010	Post cardiac arrest	HES, median, 60 (range, 48-74) NaCl, median, 60 (range, 22-75)		MAP <60, HR >100, CVP <8 mm Hg, U/O <1 mL/kg/h	6% HES 200/0.5 + 7.2% NaCl, maximum 500 mL/24 h	10	RL+ 0.9% NaCl, as needed	9
Inal et al,[40] 2010	Hypovolemia	56 (18)	APACHE: 29 (6)	ITBVI <850 mL/kg	6% HES 130/0.4, 500 mL	15	3.5% GEL, 500 mL	15
Vlachou et al,[37] 2010	Burns	42 (22)		Low U/O, HR >119, or MAP <70 mm Hg	6% HES 200/0.6, as needed	12	Hartmann's solution, according to the Parkland Formula	17
Du et al,[35] 2011	SAP	46 (11)	APACHE: 11 (4)	U/O <0.5 mL/kg/h, CVP <8 mm Hg, or SBP <90 mm Hg	6% HES 130/0.4, as needed (1:3 compared with saline solution)	21	RL, as needed	21
James et al,[4] 2011	Trauma	32 (10)		SBP <100 mm Hg	HES 130/0.4, 500 mL boluses	58	0.9% NaCl, 500 mL bolus	57
Zhao et al,[21] 2011[b]	SAP	NR	NR	NR	HES 130/0.4	20	0.9% NaCl	20
Zhu et al,[28] 2011	Sepsis	60 (9)	APACHE: 17 (2)	U/O <1 mL/kg/h	6% HES 130/0.4, 500 mL/; 6% HES 130/0.4 ± 7.5% HS, 500 mL	90	RL	45
Guidet et al,[52] 2012	Severe sepsis	66 (15)	SOFA: 9	MAP <65 mm Hg, CVP <8 mm Hg, or U/O <2 mL/kg	6% HES 130/0.4, first d: ≤50 mL/kg; 2nd-4th d: ≤25 mL/kg/d	100	0.9% NaCl, first day: ≤50 mL/kg/d; 2nd-4th d: ≤25 mL/kg/d	96
Myburgh et al,[54] 2012	Hypovolemia	63 (17)	APACHE median (range): HES, 17 (12-22) 0.9% NaCl, 17 (12-23)	HR >90, SBP <100 or MAP <75, CVP <10, PAWP <12, RV >5, Cap refill >1 s, or U/O <0.5 mL/kg	6% HES 130/0.4, 500 mL bolus, maximum 50 mL/kg/d	3500	0.9% NaCl, 500 m bolus, maximum 50 mL/kg/d	3500
Perner et al,[53] 2012	Septic shock	HES median, 66 (IQR, 56-75) GEL 67 (IQR, 56-76)	SAPS median (IQR): HES: 50 (40-60) GEL: 51 (39-62)	ICU physician's judgment	HES 130/0.42, maximum 33 mL/kg/d	400	Ringer's acetate, maximum 33 mL/kg/d	400

Abbreviations: APACHE, Acute Physiology and Chronic Health Evaluation II; Cap refill, capillary refill; CVP, central venous pressure; GEDVI, global end-diastolic index; GEL, gelatin; HES, hydroxyethyl starch; HR, heart rate; ICU, Intensive care unit; IQR, interquartile range; ITBVI, intrathoracic blood volume index; MAP, mean arterial pressure; min, minutes; NaCl, sodium chloride; NR, not reported; RL, Ringer's lactate; RV, respiratory variation; SAP, spontaneous acute pancreatitis; SAPS, Simplified Acute Physiology Score II; SBP, systolic blood pressure; SOFA, sequential organ failure assessment; SVV, stroke volume variation; U/O, urine output.

[a] Means are presented unless otherwise indicated.

[b] Abstract.

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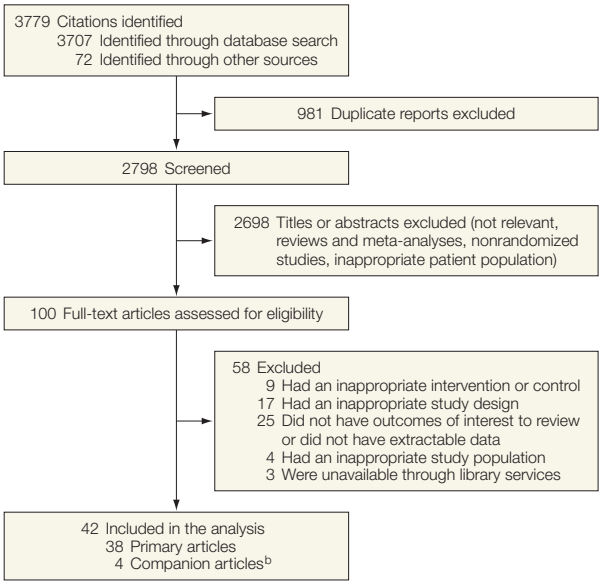
Figure 1. Study Flow Diagram[a]



[a] This flow diagram follows the Preferred Reporting Items of Systematic Reviews and Meta-Analyses (PRISMA)[14] with modifications.
[b] Companion articles represent reports of previously published analyses involving the same study population.

of hemorrhage and use of blood transfusions were conflicting with most trials providing no extractable data (Table 4). None of the included trials reported the average volume of blood loss among patients; however, 1 trial[53] involving 800 patients reported no significant difference in the incidence of severe hemorrhage. Pooled results from 5 trials[23,36,44,53,57] involving 1482 patients showed a significantly higher incidence of red blood cell transfusions in patients randomized to receive hydroxyethyl starch (RR, 1.42; 95% CI, 1.15 to 1.75; I^2, 0%); however, the transfusion volume was not reported to be different between groups in 3 trials[4,23,56] involving 162 patients (Table 4). Most trials did not systematically screen for, or report the incidence of allergic reactions to resuscitation fluids. When reported, allergies rarely (<1%) occurred[50,51,53] among 984 patients involved in 3 trials (Table 4).

Subgroup, Sensitivity and Meta-Regression Analyses

Subgroup analyses by trial region (North America vs other regions), sponsorship (industry vs other sources), publication type (peer-reviewed publication vs conference abstract), intervention (6% vs 10% hydroxyethyl starch doses), comparator (albumin, crystalloids, gelatin), patient population (sepsis vs trauma vs other populations), or the date of trial publication (before vs after Surviving Sepsis Campaign guidelines) demonstrated no major differences; however, most subgroups were subject to type II errors due to small sample sizes (eTable 7 available at http://www.jama.com). Using meta-regression we did not find a correlation between patient mortality and the duration of the study intervention or study follow-up (eFigures 1 and 2).

COMMENT

In this systematic review, we observed the overall RR for mortality associated with hydroxethyl starch to be 1.07 (95% CI, 1.00-1.13). With the exclusion of trials conducted by Boldt et al,[7,29-34] hydroxyethyl starch administration was significantly associated with increased mortality and severe kidney injury (acute renal failure and renal replacement therapy).

Hydroxyethyl starch solutions are effective volume expanders but are not localized to the circulatory system and are known to deposit in the skin, liver, muscle, spleen, endothelial cells, and kidneys of patients who receive these products.[58,59] The toxic effects on renal function have been well documented in experimental and clinical studies, but some researchers have argued that adverse effects depend on the volume and molecular weight of the hydroxyethyl starch preparations and patient population.[5] Proponents of starch solutions have argued increased safety with each newly marketed product, but evidence from randomized trials do not support these claims.[29,30,54]

Risk of bias is a major concern when adjudicating clinical trials of therapeutic interventions. The possibility of inaccurate or fraudulent data further complicates assessment and may be challenging to detect. In our systematic review, we demonstrated that inclusion of such studies can influence how the global medical community interprets a given body of literature and how exclusion of questionable studies can shift the balance of evidence toward benefit or harm. This state of affairs is not unique to trials evaluating hydroxyethyl starch; published retractions have prompted the reexamination of the superiority of multimodal pain management[60]; the association between autism and the measles, mumps, and rubella vaccine[61]; and, most recently, the efficacy of serotonin 5-HT_3 receptor antagonists for the treatment postoperative nausea and vomiting.[62]

The strengths of this review include the completeness of the search including searching multiple citation databases and trial registries, hand searching of the gray literature, and forward searching. In addition, the use of unpublished data and non-English publications increases the validity of the results. We also used an a priori published protocol and followed established methodological guidelines in the conduct and reporting of this review.

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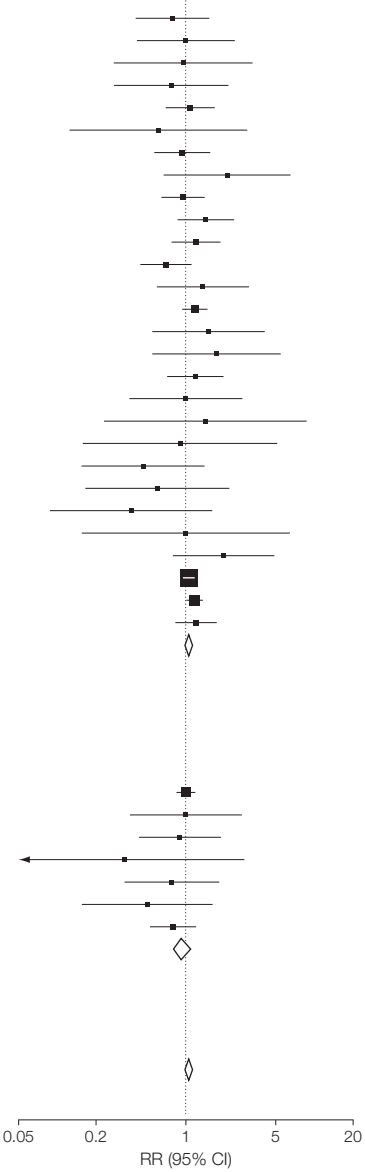
Our systematic review has limitations. We pooled trials from distinct patient populations (all of which were considered to be seriously ill requiring acute volume resuscitation), hydroxyethyl starch formulations of differing molecular weights, and competitors (eg, albumin, crystalloids, gelatin). This is, however, consistent with the clinical use of fluid resuscitation in that patients are often resuscitated with a mixture of different fluids. The subgroup analyses of mortality were susceptible to type II errors due to the relative small sample sizes, but showed a consistent trend with the main analysis. Finally, the internal validity of the trials was often unclear due to underreporting of the safeguards against the commonly identified biases, which ultimately downgraded the strength of evidence.

Although larger trials generally contribute more weight to summary ef-

Figure 2. Mortality and Hydroxyethyl Starch

Trials excluding those published by Boldt et al	HES No. of Events	HES Total	Control No. of Events	Control Total	RR (95% CI)	Weight, %
Haupt and Rackow,[24] 1982	5	9	12	17	0.79 (0.41-1.52)	0.9
Rackow et al,[50] 1989	5	10	5	10	1.00 (0.42-2.40)	0.5
Nagy et al,[23] 1993	4	21	4	20	0.95 (0.27-3.30)	0.3
Beards et al,[49] 1994	4	13	6	15	0.77 (0.28-2.14)	0.4
Berard et al,[26] 1995	32	146	31	153	1.08 (0.70-1.68)	2.0
Younes et al,[48] 1998	2	12	3	11	0.61 (0.12-3.00)	0.2
Asfar et al,[47] 2000	10	16	12	18	0.94 (0.57-1.55)	1.6
Carli et al,[51] 2000	9	85	4	79	2.09 (0.67-6.52)	0.3
Schortgen et al,[3] 2001	28	65	29	64	0.95 (0.64-1.40)	2.6
Veneman et al,[45] 2004	18	30	13	31	1.43 (0.86-2.38)	1.5
Molnar et al,[46] 2004	12	15	10	15	1.20 (0.77-1.86)	2.0
Li et al,[43] 2008	14	30	20	30	0.70 (0.44-1.11)	1.9
McIntyre et al,[22] 2008	9	21	6	19	1.36 (0.59-3.10)	0.6
Brunkhorst et al,[44] 2008	107	297	93	303	1.17 (0.94-1.47)	7.6
Heijden et al,[42] 2009	4	12	8	36	1.50 (0.55-4.11)	0.4
Dolecek et al,[41] 2009	6	26	4	30	1.73 (0.55-5.47)	0.3
Gondos et al,[38] 2010	15	50	38	150	1.18 (0.71-1.96)	1.5
Inal et al,[40] 2010	5	15	5	15	1.00 (0.36-2.75)	0.4
Vlachou et al,[37] 2010	2	12	2	17	1.42 (0.23-8.70)	0.1
Heradstveit et al,[39] 2010	2	10	2	9	0.90 (0.16-5.13)	0.1
Dubin et al,[36] 2010	3	12	7	13	0.46 (0.15-1.40)	0.3
Zhao et al,[21] 2011	3	20	5	20	0.60 (0.17-2.18)	0.2
Zhu et al,[28] 2011	3	90	4	45	0.38 (0.09-1.60)	0.2
Du et al,[35] 2011	2	21	2	21	1.00 (0.16-6.45)	0.1
James et al,[4] 2011	12	58	6	57	1.97 (0.79-4.88)	0.5
Myburgh et al,[54] 2012	597	3500	566	3500	1.05 (0.95-1.17)	35.3
Perner et al,[53] 2012	201	400	172	400	1.17 (1.01-1.36)	17.5
Guidet et al,[52] 2012	40	100	32	96	1.20 (0.83-1.74)	2.8
Subtotal (95% CI)		**5096**		**5194**	**1.09 (1.02-1.17)**	**82.0**
Total events	1154		1101			
Heterogeneity: $\tau^2 = 0.00$; $\chi^2_{12} = 19.16$; ($P = .86$); $I^2 = 0\%$						
Test for overall effect: $Z = 2.39$, ($P = .02$)						
Trials published by Boldt et al						
Boldt et al,[31] 1995	27	30	27	30	1.00 (0.84-1.18)	13.7
Boldt et al,[33] 1996[b]	6	28	6	28	1.00 (0.37-2.73)	0.4
Boldt et al,[32] 1996[a]	9	28	10	28	0.90 (0.43-1.87)	0.7
Boldt et al,[30] 1996[d]	1	15	3	15	0.33 (0.04-2.85)	0.1
Boldt et al,[29] 1996[c]	7	30	9	30	0.78 (0.33-1.82)	0.5
Boldt et al,[34] 1996[e]	3	14	6	14	0.50 (0.15-1.61)	0.3
Boldt et al,[7] 1998	31	150	39	150	0.79 (0.53-1.20)	2.3
Subtotal (95% CI)		**295**		**295**	**0.94 (0.82-1.09)**	**18.0**
Total events	84		100			
Heterogeneity: $\tau^2 = 0.00$; $\chi^2_6 = 5.82$; ($P = .44$); $I^2 = 0\%$						
Test for overall effect: $Z = 0.76$, ($P = .45$)						
Total (95% CI)		**5391**		**5489**	**1.06 (1.00-1.13)**	**100.0**
Total events	84		100			
Heterogeneity: $\tau^2 = 0.00$; $\chi^2_{34} = 25.45$; ($P = .85$); $I^2 = 0\%$						
Test for overall effect: $Z = 1.84$, ($P = .07$)						
Test for subgroup difference: $\chi^2_1 = 25.45$; ($P = .09$); $I^2 = 65.4\%$						



The varying sizes of the boxes represent the weight in the analysis. HES indicates hydroxyethyl starch. Risk ratios (RRs) are derived by a random-effects model using Mantel-Haenszel tests.

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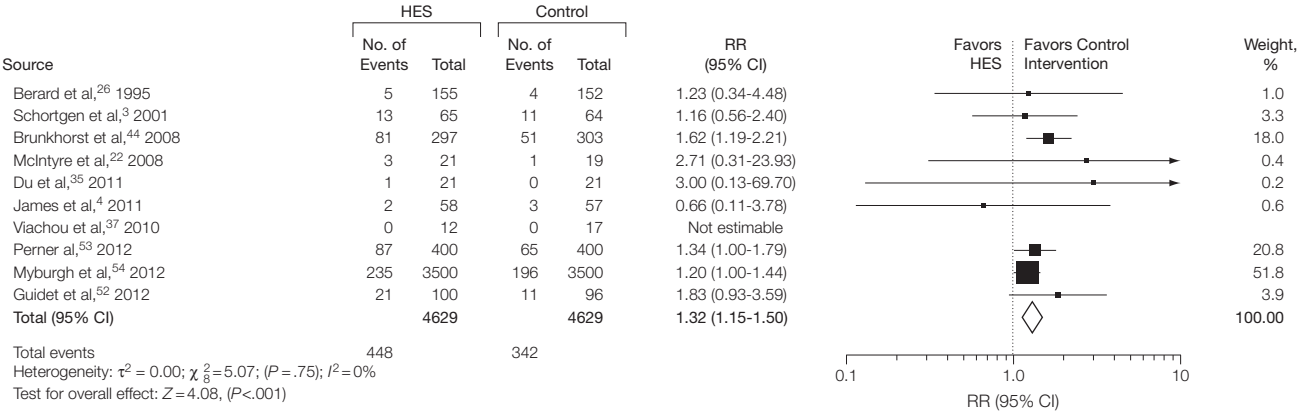
fect measures in meta-analyses, the distribution of events between groups remains an important consideration. The 5 trials that enrolled 200 or more patients accounted for 64% of the weighting in the meta-analysis of mortality. The Crystalloid versus Hydroxyethyl Starch Trial (CHEST) alone accounts for 35% of the weighting, but its exclusion neither influences the direction nor the significance of our study findings.[40]

The clinical use of colloidal starch solutions, including hydroxyethyl starch, has increased despite their higher cost relative to crystalloid solutions, lack of evidence of their clinical superiority,[8] and pervasive safety concerns.[5,63] Over the years, hydroxyethyl starch products have appeared in several resuscitation guidelines, including those of the US Hospital Consortium[64] and have often been advocated as the cornerstone of resuscitation therapy. However, recommendations are being revisited in light of major retrac-

Figure 3. Renal Replacement Therapy and Hydroxyethyl Starch



The varying sizes of the boxes represent the weight in the analysis. HES indicates hydroxyethyl starch. Risk ratios (RRs) are derived by a random-effects model using Mantel-Haenszel tests.

Table 4. Outcomes Measures[a]

Outcome or Subgroup	Studies	Study Reference No.	No. of Patients/Total No. in the Cohort: HES	No. of Patients/Total No. in the Cohort: Control	Effect Estimate (95% CI)	I^2 (Uncertainty Interval), %
RIFLE criteria						
Risk	4	4, 52-54	1861/4058	2008/4053	RR, 0.89 (0.77 to 1.03)	17 (0 to 89)
Injury	4	4, 52-54	1200/4058	1319/4053	RR, 0.93 (0.81 to 1.06)	11 (0 to 89)
Failure, acute	5	3, 44, 52-54	562/4362	464/4363	RR, 1.27 (1.09 to 1.47)	26 (0 to 71)
Failure, chronic	1	52	5/100	7/96	RR, 0.69 (0.23 to 2.09)	NE
Loss	3	35, 52, 53	8/521	9/517	RR, 0.87 (0.34 to 2.22)	0
End-stage	3	35, 52, 53	1/521	1/517	Peto OR, 1.00 (0.06 to 15.93)	NE
Secondary outcome measures						
Anuria	2	35, 37	0/33	0/38	NE	NE
Urine output, mL	11	4, 24, 25, 35-37, 42, 47, 54, 56	3431	3478	SMD, −0.15 (−0.19 to −0.10)	0 (0 to 58)
Length of stay, intensive care unit	5	21, 40, 46, 52, 54	3496	3520	MD, 0.35 (−0.20 to 0.90)	0 (0 to 71)
Length of stay, overall	6	21, 23, 26, 35, 52, 54	3653	3684	MD, 0.32 (−0.45 to 0.09)	0.00 (0 to 22)
Mechanical ventilation, d	3	23, 26, 54	3480	3504	MD, 0.28 (−0.05 to 0.61)	0 (0 to 84)
Major hemorrhage	1	53	38/400	55/400	RR, 0.69 (0.47 to 1.02)	NE
Red cell transfusion	5	23, 36, 44, 53, 57	432/739	374/743	RR, 1.42 (1.15 to 1.75)	0 (0 to 77)
Transfusion volume	3	4, 23, 56	83	79	MD, 46.31 (−610.75 to 703.37)	62 (0 to 89)
Allergy	3	50, 51, 53	1/495	0/489	MD, 7.39 (0.15 to 372.38)	NE

Abbreviations: HES, hydroxyethyl starch; MD, mean difference; NE, not evaluable; OR, odds ratio; RR, risk ratio.
[a] Does not include trials published by Boldt et al.

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tions,[64] recent trials,[52-54] and evidence from systematic reviews.[5,6] Moreover, based on available clinical data, there is no a priori reason to conclude that newer hydroxyethyl starch products with lower molecular weights are safer.[52,53] Ongoing randomized trials[65,66] will provide further clarity regarding the efficacy and safety of hydroxyethyl starch in critically ill patients.

In conclusion, among critically ill patients requiring acute volume resuscitation, use of hydroxyethyl starch, compared with other resuscitation solutions was not associated with reduced mortality. Moreover, after exclusion of 7 trials performed by an investigator whose research has been retracted because of scientific misconduct, hydroxyethyl starch was associated with a significant increased risk of mortality and acute kidney injury. Clinical use of hydroxyethyl starch for acute volume resuscitation is not warranted due to serious safety concerns.

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