REVIEW ARTICLE

A Systematic Review of the Comparative Safety of Colloids

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Hypothesis: Safety differences exist among colloids widely used for fluid management in acutely ill patients, as judged according to the comparative incidence of adverse events.

Data Sources: Colloid safety data for human subjects were sought, without language or time period restrictions, by means of computer searches of bibliographic and clinical trial databases, hand searches of medical journals and Index Medicus, inquiries with investigators and colloid suppliers, and examination of reference lists. Search terms included "colloids", "morbidity", and "mortality".

Study Selection: Controlled trials, cohort studies, pharmacovigilance studies, and prior meta-analyses were independently selected by 2 unblinded investigators. Of 189 candidate studies, 113 were included, with safety data encompassing 1.54×10^6 patients and 1.09×10^8 colloid infusions.

Data Extraction: Two unblinded investigators independently extracted data. Study limitations and confounding factors were tabulated.

Data Synthesis: With albumin as the reference colloid, the incidence rate ratio for anaphylactoid reactions was 4.51 (95% confidence interval, 2.06-9.89) after hydroxyethyl starch administration, 2.32 (95% confidence interval, 1.21-4.45) after dextran, and 12.4 (95% confidence interval, 6.40-24.0) after gelatin. Pruritus occurrence was significantly increased by hydroxyethyl starch exposure (odds ratio, 1.78; 95% confidence interval, 1.23-2.58). Artificial colloid administration was consistently associated with coagulopathy and clinical bleeding, most frequently in cardiac surgery patients receiving hydroxyethyl starch. On the basis of large-scale pharmacovigilance study results, albumin infusion resulted in a low rate of both total adverse events (3.1 to 8.6 per 10^5 infusions) and serious adverse events (1.29 per 10^6 infusions).

Conclusions: Significant safety differences exist among colloids. Therefore, conclusions regarding the clinical usefulness of colloids as a fluid class should be formed with caution.

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COLLOIDS PROMOTE RETENtion of fluid in the intravascular space, with concomitant reduction of the potential for edema that might compromise the function of organs such as the lungs, myocardium, and gastrointestinal tract.[1] The chief colloids currently in routine clinical use worldwide are albumin, hydroxyethyl starch (HES), dextran, and gelatin. Clinically available albumin is a 69-kDa protein purified from human plasma. Hydroxyethyl starch is synthesized by partial hydrolysis of amylopectin plant starch and hydroxyethylation at the C2, C3, and C6 positions of the constituent glucose molecules. Dextran is composed of naturally occurring glucose polymers synthesized by *Leuconostoc mesenteroides* bacteria growing in sucrose-containing media. Gelatin for clinical use is derived from hydrolysis of bovine collagen followed by being either succinylated or linked to urea.

All 3 artificial colloids are polydisperse molecules in a range of sizes. Hydroxyethyl starch is clinically available in an array of forms differing on the basis both of average molecular weight and extent of molar substitution, although in the United States only the HES of high molecular weight (450 kDa) of 0.7 molar substitution ratio has been used in routine fluid management. In the United States, dextran is less extensively used for fluid management than is HES, and gelatin is unavailable for clinical use.

Clinically available colloids have generally exhibited similar effectiveness in maintaining colloid oncotic pressure. Thus, colloids have often been viewed as a class of essentially interchangeable in-

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ert fluids, and selection of colloid has commonly been based on cost and convenience. Nevertheless, differences in safety profiles among colloids are well recognized.[2,3] Such differences underlie, for example, the recommended 1500 mL (20 mL per kilogram of body weight) dose limitation for HES.[4]

The clinical importance of differences in colloid safety has been debated. Firm conclusions have been difficult to draw, in part because comparative colloid safety has not been systematically reviewed. We here present the results of such a review.

METHODS

INCLUSION CRITERIA

We systematically sought all studies of acutely ill patients with data on the safety of the natural colloid albumin and the artificial colloids HES, dextran, and gelatin. Randomized controlled trials (RCTs), nonrandomized controlled trials (NCTs), cohort studies, pharmacovigilance studies (PVSs), and meta-analyses (MAs) were eligible for inclusion.

SEARCH TECHNIQUES

Clinical studies fulfilling the selection criteria were identified, without language or time period restrictions, by computer searches of the MEDLINE and EMBASE bibliographic databases, the Cochrane Controlled Trials Register, and the Cochrane Medical Editors Trial Amnesty of unpublished trials. Search terms included "colloids", "morbidity", and "mortality". Hand searches were conducted of general medical journals and Index Medicus. We contacted the authors of published clinical studies related to colloids and the medical directors of colloid suppliers and examined the reference citations from completed reviews and protocols in the Cochrane Database of Systematic Reviews, other MAs, review articles, and controlled and uncontrolled studies involving colloids.

DATA EXTRACTION AND SYNTHESIS

Two unblinded investigators (M.M.W. and R.J.N.) independently selected studies for inclusion and extracted data about study design, numbers of patients enrolled and/or infusions administered, clinical setting, fluid regimen, and major study findings, as well as study limitations and confounding factors. Differences in interpretation were resolved through discussion.

STATISTICAL ANALYSIS

Study results were generally assessed qualitatively. However, quantitative MAs were performed of data for 2 end points: anaphylactoid reactions and HES-associated pruritus. The meta-analytic methodology was generalized mixed modeling with study-level random effects. Such models are intended to accommodate expected between-study heterogeneity.

The incidence rate ratio of anaphylactoid reactions with individual colloids, as compared with albumin as reference standard, was calculated together with the corresponding confidence interval (CI) by means of random-effects Poisson regression. Pruritus associated with HES was modeled by means of random-effects logistic regression. Results were expressed as the odds ratio for occurrence of HES-associated pruritus. For both incidence rate ratio and odds ratio, the absence of the number 1 from the CI signifies a statistically significant effect.

RESULTS

INCLUDED STUDIES

Of 189 candidate studies initially identified, 113 studies published from 1944 through 2002 were included.[1-113] One RCT was excluded because of fluid overload in the albumin group.[114] Numbers of study patients, which were reported in 107 of the included studies, totaled 1.54×10^6 patients. The median number of patients per study was 60, with an interquartile range of 29 to 200. In the remaining 6 studies, the numbers of infusions were reported, and these totaled 1.09×10^8 infusions. The median number of infusions per study was 8.5×10^5 (interquartile range, $1.20\text{-}74.0 \times 10^5$). Safety data about albumin, HES, dextran, and gelatin were available from 60, 75, 17, and 25 included studies, respectively.

Twenty-one of the included studies involved acute illness generally (**Table 1**), 35 cardiac surgery (**Table 2**), 19 noncardiac surgery (**Table 3**), 5 ascites, 4 sepsis, 13 brain injury, 3 dialysis, 6 plasma exchange, and 7 acute hearing loss. (Tables summarizing studies of ascites, sepsis, brain injury, dialysis, plasma exchange, and acute hearing loss are available from the authors.) Of the cardiac surgery studies, 14 were evaluations of extracorporeal circuit pump priming; 19, volume expansion; and 2, both.

The most frequently represented study design was the RCT, which accounted for 54 studies. Twenty-eight studies were NCTs, 22 were cohort studies, 6 were PVSs, and 3 were MAs.

ALL ADVERSE EVENTS

In large-scale PVSs, the reported incidence for adverse events of any severity in albumin recipients was 6.1 to 6.8 per 10^5 infusions of 5% albumin and 3.1 to 8.6 per 10^5 infusions of 20% to 25% albumin.[7,28] For serious adverse events, an incidence of 1.29 per 10^6 infusions was reported.[111] The PVSs are generally based on spontaneous adverse event reporting and are subject to underreporting. One of these PVSs also included data for gelatin, and the reported incidence of adverse events was similar to that for albumin.[7] In a cohort study of 379 patients, the incidence of all HES-associated adverse effects was 4.5%.[42]

MORTALITY

One MA of RCTs indicated poorer survival in critically ill patients receiving albumin vs crystalloid or no albumin.[85] However, authors of a subsequent MA[110] considered RCT evidence approximately 3-fold more extensive than that of the first MA, and there was no evidence of increased albumin-associated mortality. Results of higher quality trials suggested a potential survival benefit of albumin.[110] Thus, in a multivariate analysis of blinded larger RCTs, mortality was significantly reduced by albumin (odds ratio, 0.78; 95% CI, 0.76-0.81). A large-scale PVS provided evidence that deaths after albumin administration are rare (5.24 per 10^8 infusions).[111] Hemodilution with HES was investigated in 1 RCT of patients with acute ischemic stroke.[32] The trial was stopped

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Table 1. Acute Illness

Source	Study Design	No. of Patients	Setting	Treatment	Results
Janeway et al,[5] 1944	CS	600	Hypoalbuminemia	Multiple injections of 20-25 g 25% albumin	No anaphylactoid or delayed reactions and no necropsy evidence of adverse tissue effects
Ring and Messmer,[2] 1977	NCT	2.0×10^5*	Surgical and anesthesiological practice	Albumin vs dextran (60/75 or 40) vs gelatin (urea-linked gelatin, oxypolygelatin, or modified fluid gelatin) vs HES†	Incidence rates of anaphylactoid reactions for albumin, dextran, gelatin, and HES of 0.011%, 0.032%, 0.115%, and 0.085%, respectively
Lundsgaard-Hansen and Tschirren,[6] 1980	CS	1.2×10^5*	Surgical hemorrhage and massive transfusion	Modified fluid gelatin	Incidence of anaphylactoid reactions 1.51×10^{-3} per unit of gelatin
Quast et al,[7] 1980	PVS	7.4×10^6*	Hypoalbuminemia and hypovolemia	5% vs 20% albumin vs gelatin	Incidence of all adverse events 6.12 per 10^5 infusions (95% CI, 3.51-10.68 per 10^5 infusions) for 5% albumin, 8.56 per 10^5 infusions (95% CI, 4.36-16.80 per 10^5 infusions) for 20% albumin, and 7.34 per 10^5 infusions (95% CI, 4.90-10.99 per 10^5 infusions) for gelatin
Blanloeil et al,[12] 1983	CS	4.2×10^4*	Anesthesiology practice	Modified fluid gelatin	0.028% incidence of severe anaphylactoid reactions
Weis,[16] 1983	CS	1147	Hypovolemia and other indications	Polygeline	0.78% incidence of anaphylactoid reactions
Turner et al,[28] 1987	PVS	1.5×10^6*	Clinical reactions reported to Commonwealth Serum Laboratories, Parkville, Australia, from 1976 through 1985	25% normal serum albumin vs 5% stable plasma protein solution	0.0031% and 0.0068% incidence of clinical reactions with 25% normal serum albumin and 5% stable plasma protein solution, respectively
Heilmann et al,[40] 1991	RCT	60	Fetal growth retardation and/or gestational hypertension	Hemodilution with 500 mL 10% HES (200/0.4-0.55) vs 10% HES (200/0.5) daily; both groups also received 500 mL electrolyte solution	Factor VIII reduced in both groups ($P<.02$); in HES (200/0.5) group aPTT prolonged and severe uterine bleeding in 17% of patients; in both groups, frequent HES deposition in trophoplast and placental stroma
Kaniecki et al,[42] 1991	CS	379	Transient ischemic attack, volume substitution and other indications	250-500 mL HES (200/0.5)	4.5% incidence of side effects, consisting of headache, fever, rigor, light allergic reactions, and nausea
Haws and Baum,[54] 1993	CS	24	Children with nephrotic syndrome	0.9 g/kg 25% albumin administered during 1-4 h 3 times per day plus diuretic therapy	De novo hypertension during 74% of hospitalizations, need for acute antihypertensive medication in 46%, and start or increase of maintenance antihypertensive medication in 34%
Jurecka et al,[55] 1993	CS	7	Sudden deafness, cerebrovascular insufficiency, or chronic leg ulcer	Repeated infusions of HES of medium molecular weight (200/0.5-0.6) to improve microcirculation	Six of 7 patients had developed pruritus; storage of HES was observed in skin of all patients involving a variety of skin cell types
Laxenaire et al,[57] 1994	NCT	19 593	Hypovolemia, hemodilution, rheological indications, and plasma exchange	Gelatin vs dextran (40 or 60 kDa) vs 6% or 10% HES (200/0.45-0.5) vs 4% or 20% albumin	Independent risk factors for anaphylactoid reactions included exposure to gelatin (OR, 4.81; 95% CI, 2.01-11.5) or dextran (OR, 3.83; 95% CI, 1.17-12.6) but not HES or albumin

(continued)

prematurely because of a significant increase in mortality related to cerebral edema among HES recipients.

ANAPHYLACTOID REACTIONS

In 9 studies, data were reported on anaphylactoid reactions after 3.63×10^6 total colloid infusions.[2,5,6,8,16,26,57,75,84] The pooled incidence of anaphylactoid reactions after albumin administration was 9.44 per 10^5 infusions (95% CI, 5.04-17.7 per 10^5 infusions). Infusions of all 3 artificial colloids, as compared with albumin, were associated with significantly increased anaphylactoid reactions (**Table 4**).

PRURITUS

In 1 study, there was evidence of dextran-associated pruritus in some patients.[45] Otherwise, however, reports of this adverse effect were restricted to HES exclusively. Pruritus associated with HES was reported in 14 studies involving a total of 2598 patients, of whom 2173 (83.6%) received HES and 425 (16.4%) did not.* The odds of pru-

**References 45, 52, 53, 55, 58, 59, 76, 84, 86, 95, 96, 99, 105, 106.*

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Table 1. Acute Illness (cont)

Source	Study Design	No. of Patients	Setting	Treatment	Results
Hedin and Ljungström,[75] 1997	PVS	1.5×10^6	Spontaneously reported adverse events in Sweden from 1975 through 1979 and 1983 through 1992	Dextran with vs without prophylactic hapten inhibition	0.05% incidence of grade II-V dextran-induced anaphylactoid/anaphylactic reactions without and 0.0014% with prophylactic hapten inhibition
Cochrane Injuries Group Albumin Reviewers,[85] 1998	MA	1204	RCTs of hypovolemia, burns, and hypoalbuminemia	Albumin vs crystalloid, no albumin, or lower-dose albumin	Mortality increased by albumin in trials of burns and hypoalbuminemia and all trials combined; no effect in hypovolemia trials
Gröchenig et al,[86] 1998	NCT	544	Hemodilution and volume substitution in general and vascular surgery, anesthesiology, internal medicine, and otorhinolaryngology	HES of low (70/0.5) or medium (200/0.5) molecular weight, therapy according to standards of participating centers vs no HES; control group consisted of 47 otologic patients	In HES recipients, incidence of pruritus (1%) not different from that in control group (4%)
Sharland et al,[95] 1999	CS	73	Volume expansion in ICU patients	2 L median HES (200/0.5) volume administered	Pruritus reported by 34% of patients and of these, 44% experienced severe pruritus that in many cases adversely affected quality of life, disturbed sleep, and was refractory to available remedies; in some patients pruritus persisted as long as 12 mo
Sirtl et al,[96] 1999	NCT	26	Oncologic, orthopedic, plastic, or other surgery and vascular disease	≤2 g/kg HES (200/0.5 or 450/0.7) vs 3-15 g/kg HES (200/0.5-0.6)	HES deposits observed in biopsy samples of liver, muscle, spleen, intestine, and skin; deposits persisted in skin as long as 54 mo after HES infusion, in muscle as long as 16 mo, and in intestine as long as 14 mo
von Hoegen and Waller,[111] 2001	PVS	100×10^6*	Albumin doses distributed worldwide by 9 major suppliers from 1990 through 1997	Albumin	Incidence of all spontaneously reported serious adverse events 1.29 per 10^6 infusions; no deaths probably attributable to albumin; incidence of fatal serious adverse events possibly related to albumin 5.24 per 10^8 infusions
Christidis et al,[101] 2001	CS	9	Patients referred for refractory ascites or anicteric cholestasis	Repeated infusions of 6% HES of medium molecular weight (200/0.5) for large-volume paracentesis, maintenance hemodialysis, or plasma exchange	Hepatic dysfunction worsened after HES infusion; biopsy results revealed diffuse microvacuolization of Kupffer cells; 8 patients died
Murphy et al,[106] 2001	NCT	159	Two ICUs in the United Kingdom	HES (200/0.45 or 450/0.7) vs different plasma expanders	12.6% pruritus incidence in HES recipients not significantly greater than 4% in control group; no difference in incidence related to HES type or dose
Wilkes and Navickis,[110] 2001	MA	2958	RCTs of surgery or trauma, burns, hypoalbuminemia, high-risk neonates, ascites, and other indications	Albumin vs crystalloid, no albumin, or lower-dose albumin	No effect of albumin on survival in any category of indications or across all trials combined

Abbreviations: aPTT, activated partial thromboplastin time; CI, confidence interval; CS, cohort study; HES, hydroxyethyl starch; ICU, intensive care unit; MA, meta-analysis; NCT, nonrandomized controlled trial; OR, odds ratio; PVS, pharmacovigilance study; RCT, randomized controlled trial.

*Number of infusions.

†HES molecular weight in kilodaltons and molar substitution ratio indicated (eg, 200/0.5 for 200 kDa HES of 0.5 molar substitution).

ritus were significantly increased by HES exposure (**Table 5**). The effect of HES on pruritus occurrence depended on dose. Neither HES molecular weight nor HES molar substitution exerted a statistically significant effect on pruritus.

In 1 study of patients receiving intensive care, 44% of the patients developing pruritus experienced a severe, persistent, and refractory form of the condition.[95] Pruritus associated with HES was typically delayed in onset and manifested as pruritic crises,[52,99,105] prompting patients to seek medical attention and seriously detracting from their quality of life.[95] Pruritus associated with HES is generally unresponsive to currently available forms of therapy.[52]

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Table 2. Cardiac Surgery

Source	Study Design	No. of Patients	Setting	Treatment	Results
				Pump Priming	
Palanzo et al,[11] 1982	NCT	79	CABG	3% HES* vs 4% albumin	Decline in platelet count during bypass greater in HES group ($P<.001$) and postbypass platelet count lower ($P<.02$); postbypass platelet count in HES group (136 000 ± 36 600 mL^{-1})† below normal range (140 000 to 340 000 mL^{-1})
Saunders et al,[15] 1983	RCT	20	CABG	1000 mL 6% HES (3% final concentration) in total 2000 mL vs 200 mL 25% albumin (2.5% final concentration)	In HES group, levels of liver enzymes were higher during and after bypass; mean platelet count and antithrombin III level after bypass were lower ($P = .019$ and $P = .006$, respectively) in HES than albumin group
Sade et al,[22] 1985	RCT	54	CABG, valve procedures, and CABG-valve procedures	800 mL/m^2 6% HES vs 800 mL/m^2 5% albumin added to RL to make total volume of 2500 mL; both groups received albumin intraoperatively and postoperatively for volume expansion	Intraoperative platelet count lower in HES than albumin group ($P<.01$) and pulmonary shunt fraction higher ($P<.05$); at 24 h postoperatively, HES group PT prolonged ($P<.005$)
Lumb,[25] 1987	RCT	20	CABG	500 mL 6% HES (1% final concentration) vs 150 mL 25% albumin (1.4% final concentration)	COP-PAWP gradient declined in HES ($P<.05$) but not albumin group
Himpe et al,[41] 1991	RCT	105	CABG	3.5% urea-linked gelatin vs 3% succinyl-linked gelatin vs 2.7% albumin	Need for bicarbonate during bypass higher in urea-linked gelatin than other groups ($P<.05$); intraoperative urine output lower in succinyl-linked gelatin group ($P<.05$); serum creatinine level elevated in both gelatin groups vs albumin group ($P<.05$)
Boldt et al,[46] 1992	RCT	48	CABG	250 mL 5% albumin (0.6% final concentration) vs 400 mL 20% albumin (3.6% final concentration) vs 500 mL 10% HES (2.2% final concentration) vs 500 mL 3.5% gelatin (0.8% final concentration); 5% albumin postoperatively in all groups to maintain stable hemodynamics	ADP-induced maximum platelet aggregation greater intraoperatively in 0.6% albumin and gelatin than other groups ($P<.05$) and greater in 0.6% albumin than all other groups at 24 h postoperatively ($P<.05$); collagen-induced maximum platelet aggregation greater in 0.6% albumin than other groups intraoperatively and postoperatively ($P<.05$)
London et al,[48] 1992	RCT	60	CABG and valve procedures	750 mL 10% HES and 1250 mL RL (3.8% final concentration) vs 300 mL 25% albumin and 1700 mL RL (3.8% final concentration); postoperative albumin in both groups	Intraoperative aPTT prolonged ($P<.05$) and platelet count reduced ($P<.05$) in HES vs albumin group
Videm et al,[56] 1993	RCT	63	Coronary bypass operations	6% dextran 70 with vs without 0.8% albumin	Platelet decline greater at both 4 h ($P<.05$) and 48 h ($P<.001$) postoperatively in dextran only group; blood loss during first 12 h higher by 52% in dextran only group ($P<.05$)
Tabuchi et al,[60] 1995	RCT	60	Elective CABG	400 mL 20% albumin and 1500 mL RL vs 2000 mL oxypolygelatin	Postoperative blood loss reduced by aprotinin in albumin ($P<.05$) but not oxypolygelatin group
Schneider et al,[68] 1996	NCT	267	Elective CABG	Gelatin, crystalloid prime, gentamicin, and flucloxacillin vs gelatin, crystalloid, albumin prime, and cephalothin vs crystalloid prime, gentamicin, and flucloxacillin vs crystalloid, albumin prime, and cephalothin	Incidence of acute renal failure in gelatin group receiving gentamicin and flucloxacillin (31%) higher ($P = .002$) than in corresponding crystalloid group (7%); acute renal failure more frequent ($P = .005$) in gelatin group with cephalothin (12%) than corresponding crystalloid group (2%)
Tigchelaar et al,[81,88] 1997 and 1998	RCT	36	CABG	400 mL 20% albumin and 1600 mL RL (4% final concentration) vs 500 mL 10% HES and 1500 mL RL (2.5% final concentration) vs 2000 mL 3% gelatin	On-bypass factor VIII-von Willebrand factor complex levels decreased in gelatin compared with albumin group ($P = .002$)
Herwaldt et al,[87] 1998	NCT	511	Cardiothoracic operations	6-15 mL/kg HES vs no HES	Odds of hemorrhage 37% higher in patients exposed to HES; effects of HES on bleeding dose-dependent; added costs due to hemorrhage greater than savings from lower HES acquisition cost
Keyser et al,[92] 1999	NCT	200	Consecutive adults undergoing first-time aortocoronary bypass	750 mL 10% HES and 1000 mL RL (4.3% final concentration) in prospective series of 100 patients vs 200 mL 25% albumin and 1500 mL RL (2.9% final concentration) in retrospective series of 100 similar patients	Mean mediastinal blood loss in first 18 h postoperatively for HES group (834 ± 499 mL)† greater ($P = .002$) vs albumin group (640 ± 388 mL)†

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Table 2. Cardiac Surgery (cont)

Source	Study Design	No. of Patients	Setting	Treatment	Results
Canver and Nichols,[97] 2000	NCT	887	Primary CABG	50 mL 25% albumin and 2150 mL crystalloid (0.6% final concentration) vs 500 mL 6% HES and 1700 mL crystalloid (1.4% final concentration) vs 50 mL 25% albumin and 500 mL 6% HES and 1650 mL crystallloid (final albumin and HES concentrations of 0.6% and 1.4%, respectively)	No differences in blood product use, length of stay, or mortality; however, (1) CPB duration in albumin only and albumin and HES groups longer, respectively, by 33% and 43% vs HES only group ($P<.00005$ for both comparisons), (2) 3% observed power to detect 25% mortality difference, and (3) length of stay set by Veterans Administration policy
				Volume Expansion	
Diehl et al,[9] 1982	RCT	60	CABG	6% HES vs 5% albumin during first postoperative 24 h	No differences in clotting parameters, hepatic and renal function, or alveolar-arterial oxygen gradient
Moggio et al,[13] 1983	RCT	47	CABG, valve procedures, or CABG-valve procedures	6% HES in 0.9% saline solution vs 5% albumin postoperatively to maintain cardiac index and PAWP at preoperative levels	Platelet count declined in HES ($P<.05$) but not albumin group
Kirklin et al,[17] 1984	RCT	30	CABG	6% HES vs 5% albumin to maintain left atrial pressure of 6-12 mm Hg and cardiac index $>2.0\ L \cdot min^{-1} \cdot m^{-2}$	Cumulative 24 h urine output lower in HES group ($P<.05$); PT and aPTT prolonged at 12 h, and fibrinogen level lower at 7 d in HES recipients ($P<.05$ for all comparisons)
Gallagher et al,[20] 1985	RCT	10	CABG	6% HES vs 5% albumin to maintain PAWP of 12-18 mm Hg postoperatively; prime of 1000 mL 5% albumin and 1000 mL RL for all groups; all groups received mean of 5.3 L RL intraoperatively	No differences in EVLW, PAWP, respiratory parameters, or weight gain; postoperative COP higher in albumin than crystalloid group ($P<.05$); in both groups, colloid accounted for less than half of total postoperative fluid volume
Boldt et al,[23] 1986	RCT	42	CABG	300 mL 20% albumin vs 500 mL 3% HES vs 500 mL 3.5% gelatin intraoperatively after bypass; prime of 250 mL 3.5% plasma protein solution and 1500 mL crystalloid in all groups; 400 mL 5% glucose and 100 mL 20% albumin in cases of decreased blood and filling pressure	No differences in EVLW or pulmonary shunt
London et al,[4] 1989	RCT	94	Primary or repeat CABG or valve replacement or CABG-valve procedures	10% HES in 0.9% saline solution vs 5% albumin for volume expansion during first 24 h postoperatively to maintain cardiac index $\geq 2.0\ L \cdot min^{-1} \cdot m^{-2}$ and MAP within 10% of preinduction value	No differences in respiratory and coagulation parameters
Villarino et al,[49] 1992	NCT	468	Cardiac surgery	Outbreak of postoperative nonsurgical bleeding	Patients with bleeding received more intraoperative and postoperative HES per kilogram of body weight (19.4 mL/kg vs 14.1 mL/kg; $P = .02$) for volume expansion and larger total volume of HES (1492 mL vs 875 mL; $P = .012$)
Boldt et al,[61] 1993	RCT	30	Assorted cardiac defect repair procedures in children younger than 3 y	6% HES vs 20% albumin to stabilize intraoperative hemodynamics; in both groups prime of 250 mL 5% albumin and 600 mL crystalloid	Urine output during bypass in HES group lower by 57% than that of albumin group ($P<.05$); no differences in clotting parameters
Boldt et al,[51] 1993	RCT	60	CABG	5% albumin vs 6% HES of high molecular weight (450/0.5) vs 6% HES of medium molecular weight (200/0.5) vs 3.5% gelatin to double reduced baseline PAWP intraoperatively; 250 mL 5% albumin (0.6% final concentration) in prime for all groups	Blood loss in first 24 h postoperatively higher in HES 450/0.5 than other groups ($P<.05$); maximum platelet aggregation and gradient induced by ADP, collagen, and epinephrine lower intraoperatively in HES 450/0.5 than other groups ($P<.05$); maximum platelet aggregation and gradient in HES 450/0.5 group correlated with blood loss ($P<.04$ and $P<.01$, respectively)
Mastroianni et al,[3] 1994	RCT	29	CABG or valve procedures	10% HES vs 5% albumin during first 24 h postoperatively to achieve and maintain cardiac index $>2.0\ L \cdot min^{-1} \cdot m^{-2}$ and SBP ≥ 100 mm Hg with PAWP ≤ 20 mm Hg	Mediastinal blood loss in first 24 h postoperatively 22% higher in HES than albumin group ($P<.05$); no differences in coagulation parameters
Tølløfsrud et al,[63] 1995	RCT	30	CABG	4% albumin vs 6% dextran 70 vs 3.5% gelatin to maintain heart-lung machine reservoir and stabilize postoperative hemodynamics	No differences in respiratory function or blood loss

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Table 2. Cardiac Surgery (cont)

Source	Study Design	No. of Patients	Setting	Treatment	Results
Brutocao et al,[65] 1996	RCT	47	Assorted cardiac defect repair procedures in children	6% HES vs 5% albumin to maintain adequate CVP, perfusion, and urine output	Prolongation of PT in patients receiving >20 mL/kg HES ($P = .006$); no differences in chest tube drainage or urine output
Wahba et al,[71] 1996	RCT	20	CABG	5% gelatin vs 5% albumin to maintain MAP >70 mm Hg, PAWP >10 mm Hg, and cardiac index >2.5 $L \cdot min^{-1} \cdot m^{-2}$	Intrathoracic blood volume index lower in gelatin group at 4 h postoperatively ($P<.05$); ventilation time not different
Cope et al,[73] 1997	NCT	189	Cardiac surgery	Outbreak of bleeding after CPB surgery during hospital-wide albumin shortage necessitating preferential use of HES	Rate of blood loss during first 8 h postoperatively higher ($P = .004$) in patients exposed to intraoperative HES (90 mL/h) vs no HES (59 mL/h); hemostatic agent use more frequent ($P = .007$) with intraoperative HES (35%) than no HES (14%)
Saxena et al,[79] 1997	RCT	50	CABG	6% HES vs 5% albumin after induction of anesthesia and removal of 10 mL/kg blood before bypass surgery	No differences in urine output, blood loss, or blood product use
Knutson et al,[98] 2000	NCT	444	Cardiothoracic operations	Intraoperative HES vs albumin or crystalloid	Postoperative blood loss higher ($P<.001$) in HES recipients; HES use independent predictor of bleeding ($P = .011$); postoperative use of blood products greater in HES recipients
Morgan and Berridge,[99] 2000	CS	85	Consecutive unselected cardiac surgery patients	HES vs saline solution, gelatin, or blood products	Pruritus in 22% of HES patients but none receiving other fluids ($P = .007$); pruritus classified as severe in 46% of cases; median HES volume 1400 mL in mild and 1500 mL in severe cases; median time of pruritus onset 4 wk; longest observed duration of pruritus ≥9 mo
Howard et al,[102] 2001	NCT	71	ICU care after cardiac surgery	Rapid infusion of 250-500 mL 4% albumin vs 0.9% saline solution across 10-30 min	Four cases of hypotension in albumin group vs none in crystalloid group ($P = .12$); however, effect correlated with use of angiotensin-converting enzyme inhibitors ($P = .04$)
Petroni et al,[107] 2001	RCT	28	Elective cardiac surgery requiring CPB	6% HES in RL vs 5% albumin for intraoperative and postoperative volume expansion as long as 24 h after surgery	No differences in thromboelastographic results, chest tube output, or blood product use
			Both Pump Priming and Volume Expansion		
Tabuchi et al,[60] 1995	NCT	71	Elective CABG	Gelatin-primed circuit and no perioperative limit on total gelatin use with vs without aprotinin	Postoperative blood loss linearly correlated ($P<.002$) with volume of gelatin administered
Wilkes et al,[109] 2001	MA	653	RCTs of cardiac surgery	HES of high or medium molecular weight vs albumin	Increased postoperative bleeding with use of HES for either pump priming ($P<.05$) or volume expansion ($P<.05$)

Abbreviations: ADP, adenosine diphosphate; aPTT, activated partial thromboplastin time; CABG, coronary artery bypass graft; COP, colloid oncotic pressure; CPB, cardiopulmonary bypass; CS, cohort study; CVP, central venous pressure; EVLW, extravascular lung water; HES, hydroxyethyl starch; ICU, intensive care unit; MA, meta-analysis; MAP, mean arterial pressure; NCT, nonrandomized controlled trial; PAWP, pulmonary arterial wedge pressure; PT, prothrombin time; RCT, randomized controlled trial; RL, Ringer lactate; SBP, systolic blood pressure.

*HES molecular weight in kilodaltons and molar substitution ratio indicated (eg, 200/0.5 for 200 kDa HES of 0.5 molar substitution).

†Mean ± SD.

COAGULOPATHY

Results of numerous studies indicate that HES administration can lead to reduction in circulating factor VIII and von Willebrand factor levels, impairment of platelet function, prolongation of partial thromboplastin time and activated partial thromboplastin time, and increase in bleeding complications.† Coagulopathy and hemorrhage associated with HES are often encountered in cardiac surgery, a setting in which susceptibility to such complications is heightened by transient acquired platelet dysfunction resulting from the procedure. Thus, in cardiac surgery studies with albumin as the control, HES has resulted in platelet depletion and dysfunction, prothrombin time and activated partial thromboplastin time prolongation, and increased postoperative bleeding.‡ One NCT of 444 patients revealed significant increases in blood product use, as well as postoperative blood loss, in patients receiving HES

†*References 27, 29, 34, 40, 61, 62, 69, 78, 80, 82, 94, 103, 104.*

‡*References 3, 11, 13, 15, 17, 46, 48, 50, 65, 92.*

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Table 3. Noncardiac Surgery

Source	Study Design	No. of Patients	Setting	Treatment	Results
Schöning and Lorenz,[8] 1980	RCT	450	Orthopedic surgery	Preoperative gelatin without vs with H_1-receptor vs H_2-receptor antagonist premedication	No anaphylactoid reaction in any group
Schöning et al,[19] 1984	RCT	300	Orthopedic surgery	10% HES* (200/0.5) vs 6% dextran 70	Cardiac arrest occurred in 1 of 116 patients (0.9%; 95% CI, 0.02%-4.96%) randomized to dextran despite hapten inhibition
Harris et al,[21] 1985	RCT	154	Total hip replacement	10 mL/kg 10% dextran of low molecular weight during operation and 7.5 mL/kg for 2 days postoperatively plus pneumatic compression vs 1.2 g/d aspirin vs 0.3 g/d aspirin	Excessive bleeding on day of operation in 3 dextran recipients during early part of study prompted dextran dose reduction to maximum of 500 mL intraoperatively for remaining patients
Dawidson et al,[24] 1987	RCT	17	Kidney transplants from living related donors	0.5 g/kg albumin vs dextran 40 during surgery	Postoperative urine volume and serum creatinine level not different between groups
Paull,[26] 1987	CS	5745	Major gynecological surgery or cesarean section	1000 mL dextran 70 in first 24 h and 500 mL per 24 h thereafter until removal of intravenous cannula	0.26% (95% CI, 0.22%-0.30%) incidence of dextran-induced anaphylactoid reactions
Gold et al,[36] 1990	RCT	40	Abdominal aortic aneurysm surgery	1 g/kg 5% albumin vs 6% HES before completion of vascular anastomoses	No differences in coagulation parameters, blood loss, or RBC use
Prien et al,[1] 1990	RCT	18	Abdominal surgery	10% HES vs 20% albumin to maintain CVP at preoperative level	Intraoperative intestinal edema greater in HES recipients ($P \leq .05$)
Heilmann et al,[39] 1991	RCT	207	Consecutive women undergoing cesarean section	3×500 mL 6% HES of medium molecular weight (200/0.62) vs 3×5000 IU/d heparin	No differences in blood loss, bleeding complications, transfusion requirements, or reoperation
Bernard et al,[64] 1996	NCT	24	Renal transplantation	Donor care involved infusion of HES vs no HES	Urinary output lower ($P < .05$) in patients receiving HES (1001 ± 1028 mL)† vs no HES (2097 ± 1490 mL)† and dopamine requirement higher (16 ± 12 vs 4 ± 4 μg/kg · min; $P < .05$)†; 25% frequency of osmotic nephrosis-like lesions in both groups; no difference in serum creatinine level at 1, 3, and 6 mo after transplantation
Cittanova et al,[66] 1996	RCT	69	Kidney transplants from brain-dead donors	6% HES of medium molecular weight (200/0.60-0.66) as much as 33 mL/kg followed by gelatin if needed vs gelatin only for plasma volume expansion in kidney donors	During first 8 d after transplantation, 33% of kidney recipients required hemodialysis or hemodiafiltration in HES-gelatin group, as compared with 5% of gelatin-only patients ($P = .029$); serum creatinine concentrations lower in gelatin-only group ($P = .009$)

(continued)

for volume expansion.[98] The effects of HES on clinical bleeding in cardiac surgery patients depend on dose; however, excessive postoperative bleeding has been reported with HES doses less than the recommended maximum.[87]

Results of 1 RCT suggested that postoperative bleeding might be greater in patients receiving HES of high rather than medium molecular weight.[50] This result was not supported, however, by results of 1 NCT of 200 patients showing postoperative blood loss significantly greater after pump priming with HES of medium molecular weight than with albumin.[92] Furthermore, in 1 MA of RCTs, bleeding was increased by HES, as compared with albumin, and the effects of HES of high and medium molecular weight were similar.[109]

Dextran, as compared with albumin, has been shown to reduce platelets and increase postoperative bleeding in cardiac surgery patients.[56] Postoperative blood loss was linearly correlated with the volume of gelatin used to prime the extracorporeal circuit.[60]

RENAL FAILURE

All 3 artificial colloids have been associated with renal impairment, and HES has been demonstrated to increase sensitive markers of renal tubule damage in surgical patients.[74,93] In 1 RCT of sepsis patients, HES exposure was recently shown to be an independent risk factor for acute renal failure.[108]

In the renal transplantation setting, HES reduced urinary output, increased creatinine levels and dopamine requirement, and increased the need for hemodialysis or hemodiafiltration.[64,66] By contrast, in 1 NCT, no significant difference was evident in delayed graft function after renal transplantation with administration of HES to the donor.[89]

In a cohort study of patients with acute ischemic stroke, 4.7% experienced acute renal failure associated with dextran infusion.[72] Gelatin, as compared with albumin as pump prime in cardiac surgery, elevated creatinine levels.[41]

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Table 3. Noncardiac Surgery (cont)

Source	Study Design	No. of Patients	Setting	Treatment	Results
Dehne et al,[74] 1997	RCT	25	Hypovolemia in surgical patients	12 mL/kg 10% HES vs no HES postoperatively	In HES group, postoperative increases in α_1-microglobulin, Tamm-Horsfall protein, and brush border *N*-acetyl-β-glucosaminidase; no glomerular function differences
Bothner et al,[84] 1998	RCT	750	Minor elective surgery	6% HES (200/0.5) vs RL for intraoperative and postoperative volume expansion	621 ± 351 mL† total HES volume infused; no differences in incidence of anaphylactoid reactions or pruritus
Deman et al,[89] 1999	NCT	109	Renal transplantation	6% HES of medium molecular weight (200/0.5) vs HES of high molecular weight (450/0.7) vs gelatin-albumin administered to donor 12-24 h before organ retrieval	No differences in incidence of delayed graft function; higher postoperative creatinine levels in HES of high vs medium molecular weight groups
Karoutsos et al,[91] 1999	RCT	42	ASA grade I patients undergoing total hip or knee replacement	3.5% modified gelatin solution (35 kDa) vs 6% HES of medium molecular weight (200/0.62) vs 5% albumin	Hypercoagulability demonstrated at thromboelastography in gelatin but not other groups ($P<.001$)
Kumle et al,[93] 1999	RCT	60	Major abdominal surgery	6% HES of low (70/0.5) vs medium (200/0.5) molecular weight vs modified gelatin (35 kDa) for volume replacement	α_1-microglobulin increased 3.3-fold and 2.0-fold in patients <65 y and >65 y, respectively, receiving HES of low molecular weight ($P<.05$ for both age categories) but not other groups
Omar et al,[94] 1999	NCT	50	Prostatectomy for benign prostatic hyperplasia	15 mL/kg 6% HES (200/0.5) vs equal volume of 5% albumin during operation	Factor VIII:C levels and platelet aggregation declined, respectively, by 25% and 31% in HES but not albumin group ($P<.05$ for both comparisons)
Torchia and Danzinger,[100] 2000	NCT	154	Colorectal surgery	Albumin vs no albumin perioperatively; <50 mL of albumin administered in 42% of albumin recipients	Albumin administration an independent risk factor for infection
Huraux et al,[103] 2001	NCT	40	Abdominal surgery	Intraoperative infusion of 20 vs 30 mL/kg 6% HES of medium molecular weight (200/0.6)	Both HES doses induced thrombocytopenia, prolonged aPTT, and reduced levels of factor VIII:C and von Willebrand factor ($P<.05$ for all comparisons)
Trull et al,[113] 2002	RCT	60	Liver transplantation	In patients receiving tacrolimus or cyclosporine, fluid replacement with albumin vs gelatin during first 2 postoperative weeks; all groups received gelatin in cases of bleeding >1000 mL/h	Serum creatinine level elevated in recipients of gelatin and tacrolimus, compared with that in other groups ($P<.001$); acute rejection risk higher in tacrolimus plus albumin group ($P = .03$), indicating tacrolimus binding by albumin

Abbreviations: aPTT, activated partial thromboplastin time; ASA, American Society of Anesthesiology; CS, cohort study; CVP, central venous pressure; HES, hydroxyethyl starch; NCT, nonrandomized controlled trial; RBC, red blood cell; RCT, randomized controlled trial; RL, Ringer lactate.

*HES molecular weight in kilodaltons and molar substitution ratio indicated (eg, 200/0.5 for 200 kDa HES of 0.5 molar substitution).

†Mean ± SD.

CIRCULATORY DYSFUNCTION

The occurrence of circulatory dysfunction marked by increased plasma renin activity and aldosterone has been investigated in patients who have ascites and are undergoing large-volume paracentesis. The incidence of circulatory dysfunction was significantly higher after infusion of dextran than of albumin in 2 RCTs[38,67] but not in a third.[47] Circulatory dysfunction was also more frequent in patients receiving gelatin than in those receiving albumin.[67]

HEPATIC DYSFUNCTION

Repeated infusion of HES in conjunction with dialysis resulted in the development of ascites that necessitated Denver shunt implantation in 1 case.[18] In 1 recent study, HES deposition in hepatic Kupffer cells was associated with worsening of hepatic dysfunction after HES infusion.[101] Pump priming with HES, as compared with albumin, during cardiac surgery has been found to increase levels of liver enzymes during and after cardiopulmonary bypass surgery.[15]

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TISSUE DEPOSITION

Hydroxyethyl starch is deposited in a variety of tissues, including skin, liver, muscle, spleen, intestine, trophoblast, and placental stroma.[18,40,55,96,101] Such deposition often has been described in association with pruritus.[55,96] Tissue deposits persist as long as 54 months after HES administration.[96] Organ deposition of dextran has been reported in 1 NCT of patients undergoing long-term hemodialysis.[35] Tissue deposition of administered albumin has not been detected at necroscopic examination.[5]

COMMENT

The major conclusion emerging from this systematic review is that there are clinically important differences in safety among colloids. Many of the differences have been demonstrated between albumin and HES, possibly because these 2 colloids have been more extensively investigated than have dextran and gelatin.

The incidence of adverse events in albumin recipients was low. Albumin administration was not consistently associated with any characteristic types of adverse events. This observation is perhaps unsurprising, because albumin infusion serves to replenish the normal endogenous colloid. Although albumin is isolated from human plasma, we could identify no evidence of viral disease transmission attributable to albumin.

Bleeding associated with artificial colloid administration has been widely reported.* Such complications have been particularly frequent in the cardiac surgery setting, necessitating increased blood product use and increased costs of care.[87,98] Bleeding complications can be particularly troublesome because of the long half-life of HES and because discontinuation of HES infusion cannot immediately resolve coagulopathy.

Although potentially life threatening, anaphylactoid reactions were relatively infrequent for all colloids. Hydroxyethyl starch, as compared with albumin, more than quadrupled the incidence of anaphylactoid reactions, whereas dextran more than doubled them. The incidence of these reactions in recipients of gelatin was greater by more than an order of magnitude than that after albumin infusion. Because artificial colloids are derived from nonhuman source materials, they may be recognized as foreign and hence are more likely to provoke an immune-mediated response. The foreign nature of artificial colloids may also hinder metabolic clearance and promote tissue deposition.

Although HES has been widely used for several decades, HES-related pruritus has been widely described only since the early 1990s.[45] Its late recognition as a clinical entity appears to be at least partly because of the lengthy delay in onset of symptoms, in many cases occurring after discharge. This adverse effect was initially characterized in otologic patients receiving relatively high HES doses to improve microcirculation. Besides otologic indications, we identified evidence of HES-associated pruritus in studies of general[96] and cardiac[99] surgery, patients receiving intensive care,[95,106] and subarachnoid hemorrhage.[105] In our MA, the pooled odds of pruritus were significantly increased by HES exposure. Although the effect was dose related, many patients receiving less than the recommended 20 mL/kg HES maximum were affected.[95,99] In a cardiac surgery study, more than half of the patients developing pruritus had received less than the recommended HES maximum.[99]

We compiled substantial evidence linking HES exposure to increased risk of renal failure. This effect has been characterized in the settings of surgery,[74,93] sepsis,[108] and kidney transplantation.[64,66] Adverse effects of HES in kidney transplantation have, however, been controversial.[89]

Outside the United States, HES products of varying molecular weight and/or molar substitution have been introduced. It has often been argued that adverse effects of HES are primarily attributable to preparations of higher molecular weight and greater molar substitution.[61,70] The basis for such putative differences is the more rapid clearance of HES of lower molecular weight and less highly substituted forms. In our MA, neither HES molecular weight nor molar substitution significantly affected the odds of pruritus. More broadly, our systematic review failed to reveal consistent differences among HES preparations with respect to safety.

On the basis of extensive evidence, albumin appears to be in general the safest colloid of the 4 we reviewed. In some settings, other factors such as the desirability of anticoagulant activity might militate in favor of artificial colloids. In any case, results of our review suggest the need to consider the contrasting safety profiles of colloids in clinical decision making.

Table 4. Pooled Incidence Rate Ratios for Anaphylactoid Reactions

Colloid	Pooled Incidence Rate Ratio*	95% Confidence Interval
Hydroxyethyl starch	4.51	2.06-9.89
Dextran†	2.32	1.21-4.45
Gelatin	12.4	6.40-24.0

*Relative to albumin: 1 study[12] was excluded from pooled incidence rate ratio calculation because reported data were restricted to severe anaphylactoid reactions only.

†Includes data from 2 dextran studies[57,75] in which some patients received hapten inhibition and others did not; use of hapten inhibition in the remaining 2 dextran studies[2,26] was unspecified.

Table 5. Pooled Odds Ratios for Pruritus Associated With HES

Variable	Pooled Odds Ratio	95% Confidence Interval
HES exposure (HES vs no HES)	1.78	1.23-2.58
HES dose (100-g increment)	1.46	1.38-1.55
HES molecular weight (450 kDa vs 200 kDa)	1.32	0.55-3.16
HES molar substitution ratio (≤0.5 vs >0.5)	1.19	0.54-2.60

Abbreviation: HES, hydroxyethyl starch.

References 3, 21, 27, 40, 49, 50, 56, 60, 62, 73, 87, 92, 98, 104, 109.

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