Safety of Modern Starches Used During Surgery

Philippe Van Der Linden, MD, PhD,* Michael James, MB ChB, PhD, FRCA, FCA(SA),‡ Michael Mythen, MD FRCA,‡§‖ and Richard B. Weiskopf, MD¶

Various hydroxyethyl starch (HES) preparations have been used for decades to augment blood volume. There has been concern recently regarding possible adverse outcomes when using HES in the intensive care setting, especially in patients with septic shock. However, the pharmacokinetic and pharmacodynamic properties of HES preparations depend on their chemical composition and source material. Thus, different clinical conditions could result in differing effectiveness and safety for these preparations. Consequently, we assessed the safety of tetrastarches when used during surgery, using a formal search, that yielded 59 primary full publications of studies that met a priori inclusion criteria and randomly allocated 4529 patients with 2139 patients treated with tetrastarch compared with 2390 patients treated with a comparator. There were no indications that the use of tetrastarches during surgery induces adverse renal effects as assessed by change or absolute concentrations of serum creatinine or need for renal replacement therapy (39 trials, 3389 patients), increased blood loss (38 trials, 3280 patients), allogeneic erythrocyte transfusion (20 trials, 2151 patients; odds ratio for HES transfusion 0.73 [95% confidence interval = 0.61–0.87], $P = 0.0005$), or increased mortality (odds ratio for HES mortality = 0.51 [0.24–1.05], $P = 0.079$). (Anesth Analg 2013;116:35–48)

The relative merits of colloids or noncolloidal salt solutions when used for blood volume augmentation remain controversial and appear to be context sensitive. Various starch preparations have been used for this and similar purposes in many clinical circumstances for several decades.[1–3] Our understanding of the pharmacokinetic and pharmacodynamic properties of hydroxyethyl starches (HES) has evolved[4] so that we now appreciate that both properties vary depending on the starch source and on their chemical composition: degree of substitution, molecular location of substitution, average molecular weight, and molecular weight distribution.[5] Consequently, the manufacture of HES has progressed from hetastarches (molar substitution ratio, 0.7), to pentastarches (molar substitution ratio, 0.5), and then to tetrastarches (molar substitution ratio, 0.4 or 0.42). In addition, it is reasonable to consider that different clinical conditions could result in differing effectiveness and safety for these preparations.

From the *Service D'Anésthesiologie–Réanimation, CHU Brugmann, Bruxelles, Belgium; †Department of Anaesthesia, University of Cape Town, Cape Town, South Africa; ‡University College London; §University College London Hospitals NHS Foundation Trust/University College London and Royal Free London NHS Foundation Trust, Research Support Centre; ‖Department of Health, Enhanced Recovery Partnership, London, United Kingdom; and ¶Department of Anesthesia and Perioperative Care, University of California, San Francisco, San Francisco, California.

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Address correspondence to Richard B. Weiskopf, MD, Department of Anesthesia and Perioperative Care, University of California, San Francisco, Box 0648, San Francisco, CA 94143. Address e-mail to richardweiskopf@hotmail.com; rbw@itsa.ucsf.edu

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The presence of an intact tight glycocalyx/vascular endothelial junction in health provides for the retention of colloids, whereas its impairment in various disorders permits the extravasation of colloids, thus simultaneously increasing the volume of colloid required for resuscitation to that approaching salt solutions[6,7] and offering the possibility of adverse effects because of its extravascular presence. The induction of hypervolemia in healthy individuals has also been reported to allow extravasation of colloids.[8]

Recently, there has been concern regarding possible adverse outcomes when using starch preparations in the intensive care setting, especially in septic patients.[9] Prospective, randomized clinical trials[10,11] and retrospective analyses[9] have suggested that the use of some HES preparations in sepsis adversely affects renal and coagulation function more than does other IV fluids. However, preliminary results from another prospective, randomized study (Crystalloids Morbidity Associated in Severe Sepsis [CRYSTMAS])[12] indicated that a lesser volume of a 6% tetrastarch was required than 0.9% sodium chloride (NaCl) to produce hemodynamic stability, without having a difference between the 2 in renal or coagulation function or mortality in patients with severe sepsis. Two large prospective trials have addressed this issue as well: one evaluating a potato-derived 6% 130/0.42 tetrastarch (6S)[13] recently reported that 90-day mortality in septic shock is increased in comparison with crystalloid administration. The other, evaluating a maize-derived 130/0.4 tetrastarch, remains in progress (Crystalloid Versus Hydroxyethyl Starch Trial [CHEST]).[14]

HES is used widely for intravascular volume maintenance or augmentation during surgery. The effectiveness and safety of HES is likely to differ when used in relatively healthy people rather than in septic patients because endotoxic shock or sepsis disrupts vascular integrity in experimental animals[15] and patients,[16] causing altered distribution of large molecules.[17] A recent meta-analysis assessed a 130/0.4 tetrastarch in acutely ill and perioperative patients.[18] However, we were unaware of any formal analysis of the data relating to safety emanating from prospective

randomized clinical trials using modern tetrastarch products solely in the acute surgical setting, that excluded publications that have been withdrawn. Consequently, we undertook to assess the safety (but not effectiveness) of tetrastarches when used during surgery.

METHODS

We used a formal search strategy to assess the safety of tetrastarches when used during surgery. We decided a priori to include in our evaluation data only from randomized trials and to focus on the clinical outcomes of renal function, coagulation function, and mortality. For coagulation, our primary measure was that of blood loss. For a secondary measure, we assessed the frequently used surrogate for blood loss: red cell transfusion (volume and fraction of patients receiving red cell transfusion). We decided a priori to extract laboratory assessments of coagulation function, but not to use those as a clinical outcome owing to the uncertain and controversial relationship in the surgical setting between the laboratory and the clinical findings and the greater importance of the latter. For renal assessment, we evaluated the need for renal replacement therapy (RRT) and because of its low incidence and the well-established relationship of renal function to serum creatinine, change or absolute values of the latter as well. Data for urine output were also sought but deemed to be of uncertain clinical importance and, thus, of lesser value than RRT or creatinine, because of the data being influenced by numerous factors other than specific renal impairment. We searched for volunteer trials and clinical trials in adults or children undergoing general and/or regional anesthesia for elective and emergency surgery, and for trauma and burns, where patients received a tetrastarch: either a waxy maize-derived HES 130/0.4 or a potato-derived HES 130/0.42 compared with another intervention such as another colloid, a crystalloid, a blood product, a vasoactive drug, or no other treatment. We searched in all languages. All clinical outcomes were included to avoid missing data of interest that might not have been included in the title, abstract, or key words. We searched MEDLINE, CENTRAL (Cochrane Central Register of Controlled Trials), and EMBASE from January 1, 1997, to December 1, 2011, using the search terms and strategies indicated in Appendix 1. We included all phase 1 to phase 4 trials and randomized clinical trials in patients or volunteers. Volunteer studies were included only if the HES and comparator were given to the volunteer and excluded if the volunteer only supplied a blood sample for ex vivo manipulation and testing. We included studies in which the trial population underwent surgery, trauma, or burns, even when the fluid was given shortly beforehand (e.g., coload for regional anesthesia) or shortly afterward. We excluded trials where the population was not surgical (e.g., cirrhosis, sepsis, stroke) and assessed only primary reports of data and not reviews or meta-analyses.

To maximize sensitivity, the search did not attempt to remove duplicate data, except where exactly the same trial or publication appeared on more than one database. Hence, we included data that appeared in a peer-reviewed journal as a conference abstract even when a similar (but not identical) reference appeared later in fully published form. Duplicate data were removed later, when all retrieved publications were examined and evaluated. We did not contact authors to attempt to include any data that they may have gathered, but did not publish, and consequently had not been peer reviewed. We included as well trials that were already known to any of us if they met our inclusion criteria, but had not been found by the electronic searches (Appendix 2).

The group met in person on 3 occasions and discussed by telephone and electronic communication the potential value of performing this work to plan the effort, strategy, and organization; to evaluate the results; and to write the article. All of us reviewed the data and contributed to the writing of the article.

Statistics

Differences in proportions (and odds ratios [ORs], and 95% confidence intervals [CIs]) between those patients receiving a tetrastarch and those receiving a comparator for mortality, for transfusion of allogeneic red cells, and need for RRT were assessed by Fisher exact test (Instat 3 for Macintosh, V3.0b; GraphPad Software, Inc., La Jolla, CA).

RESULTS

The search yielded 213 publications of which 59 were determined to meet the a priori inclusion criteria in the acute surgical environment (excluding abstracts and duplicate publications). These studies included 4529 unique patients who had been randomly allocated to be treated with a tetrastarch ($n = 2139$) or a comparator ($n = 2390$). Brand names of various HES products are listed in Appendix 3.

Mortality

Twenty-one studies reported mortality for 1918 randomly allocated patients. There were 11 deaths reported in the 956 patients given a tetrastarch (1.15% [95% CI, 0.57%–2.05%] and 22 deaths in the 982 patients given a comparator (2.24% [1.41%–3.37%]. The OR for mortality for HES administration versus all comparators was 0.51 ([0.24–1.05]; $P = 0.079$; Fig. 1).

Coagulation

Of all reports meeting the a priori criteria, 50 publications randomly allocated patients to receive a tetrastarch

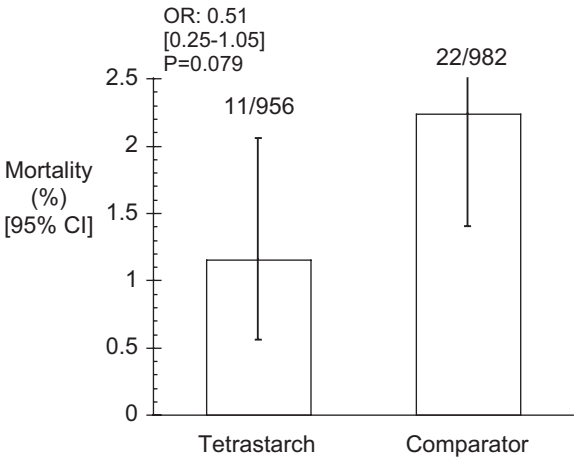

Figure 1. Mortality from all publications reporting such data. Bars are 95% confidence intervals.

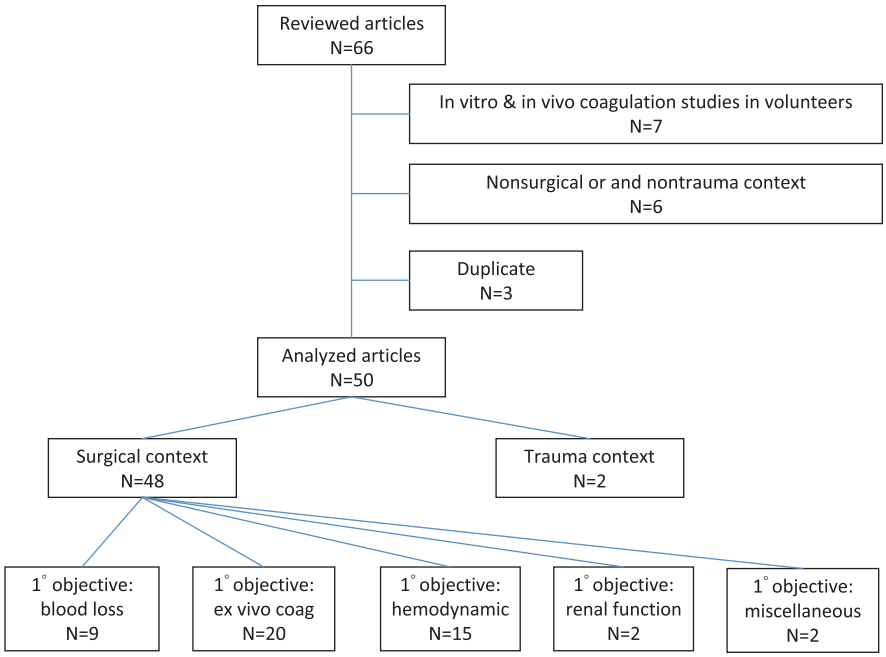

Figure 2. Flow chart of reviewed and analyzed publications related to coagulation.

or a comparator that included data regarding blood loss, red cell transfusion, or laboratory studies of coagulation (Fig. 2). For analysis of effects of tetrastarch on coagulation and blood loss, studies of trauma were analyzed separately due to trauma-induced changes of coagulation.[19] Trials performed in a pure surgical context were evaluated according to their primary outcome measure (see the subsequent paragraphs). Among the 48 surgical studies analyzed, there were 38 randomized clinical trials with data for blood loss, containing 1602 patients randomly allocated to receive a tetrastarch and 1678 allocated to be given another HES, other colloid, or a crystalloid solution (for the purposes of this review, we considered MP4OX, a hemoglobin-based oxygen carrier [HBOC], as a colloid, in as much as it was used in that manner and not for its oxygen-carrying property). There was no suggestion that patients given a tetrastarch had increased blood loss relative to those given other fluids (Fig. 3). Another 3 publications reported information regarding transfusion, but not blood loss, that included 96 patients randomly allocated to receive a tetrastarch and 125 to receive a comparator. In these 3 studies, use of a tetrastarch was not associated with an increase in blood use when compared with albumin or Ringer's lactate solution but was associated with a decrease in the number of patients transfused when compared with HES 200/0.5.

Nine prospective randomized studies compared a saline-based 6% tetrastarch from waxy-maize origin (130/0.4) with other fluids using blood loss as the primary objective (Table 1). All but 1 concerned cardiac surgery, including 2 evaluating pediatric patients and 1 off-pump coronary artery bypass grafting. The other study assessed patients undergoing urological cancer surgery. Only 1 study claimed to be double blind, but the authors did not describe the blinding process.[20] None reported an increase in intra- and/or postoperative bleeding. All studies described the transfusion trigger that was applied to patients. The volume of packed red blood cells transfused and the incidence of

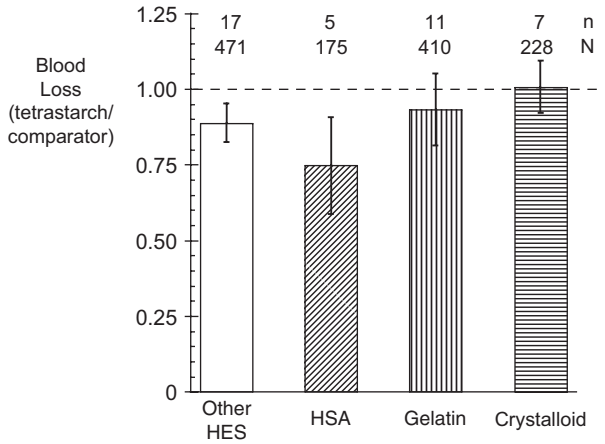

Figure 3. Ratio of blood loss for patients given a tetrastarch to the blood loss for patients given comparators. The bars are the mean values (95% confidence intervals) of the mean or median group data reported in all publications providing blood loss data for groups of 5 or more trials. *n* = number of publications providing data; *N* = number of patients in those trials who were given a tetrastarch; HSA = human serum albumin. Other comparators with <5 trials in a group were MP4OX (a hemoglobin-based oxygen carrier): 2 trials of 385 patients, average blood loss ratio = 0.924; fresh frozen plasma 1 trial, N = 21; blood loss ratio = 1.14; dextran 70 trial, N = 20, blood loss ratio = 0.975. No statistical analyses were performed.

allogeneic transfusion were comparable between patients randomized to the tetrastarch and those to the control fluid in all reports, except in 1 pediatric study where a significantly smaller fraction of children was exposed to transfusion in the tetrastarch group than that in the 4% albumin group.[21]

Twenty prospective randomized studies compared 6% tetrastarches with other fluids using ex vivo coagulation variables as the primary outcome measure. Among these studies, 13 presented data on perioperative blood loss and 9 on perioperative blood transfusion (Table 2). Only 1 trial

Table 1. Studies Using Blood Loss as the Primary Objective

Authors	Surgery	Starch/comparator	Volume (mL)	No. patients (N)	Blood loss (mL)	Volume packed red blood cells	% Transfused
Kasper et al.[54]	Cardiac	130/0.4	3500 (2000–4500)	59	660 (380–1440)	1 (0–6) U	32%
		HES 200/0.5[a]	2500 (1850–3250)	58	705 (330–1750)	1 (0–6) U	32%
Van der Linden et al.[52]	Cardiac	130/0.4	48.9±17.2 mL/kg	64	544±305[b]	0 (0–6) U	38%
		MF gelatin	48.9±14.6 mL/kg	68	504±327[b]	0 (0–6) U	31%
Ellger et al.[65]	Major	130/0.4	50 mL/kg	20	2563 (750–5500)	1.7 (0–6) U	NR
	Abdominal	HES 200/0.5+MF gelatin	30 + 20 mL/kg	20	2430 (1000–4000)	1.3 (0–4) U	NR
Chong Sung et al.[66]	Cardiac	130/0.4	10 mL/kg	21	9.9±4.8 mL/kg	7.5±6.0 mL/kg	81%
	Pediatric	Fresh frozen plasma	10 mL/kg	21	8.7±3.9 mL/kg	7.6±6.2 mL/kg	81%
Boks et al.[67]	Cardiac	130/0.4	1000	90	1768±75	586±55 mL	NR
		MF gelatin	1300–1500	90	1921±89	582±57 mL	NR
Ooi et al.[68]	Cardiac	130/0.4	1942±1046	45	567±281	NR	89%
		MF gelatin	1973±729l	45	596±337	NR	93%
Vanhoonacker et al.[20]	Cardiac	130/0.4	1500	82	9.4±6.1 mL/kg	0.77±0.90 U	NR
		MF gelatin	1500	72	7.8±5.0 mL/kg	0.63±1.08 U	NR
Hanart et al.[21]	Cardiac	130/0.4	50 (37–50) mL/kg	60	19 (9–31) mL/kg[b]	18 (0–40) mL/kg	57%
	Pediatric	4% albumin	50 (45–50) mL/kg	59	25 (13–32) mL/kg[b]	29 (6–42) mL/kg	78%*
Lee et al.[69]	Cardiac	130/0.4	1458±465[c]	53	978±347	2.1±1.6 U	27%
	Off pump	Balanced crystalloid	8342±1794	53	1028±389	1.6±1.2 U	23%

Studies for which blood loss was the primary end point. All studies of randomly allocated patients. Author's name in italics indicates publications that specifically indicated that the trial was double blinded. All values are those from the published reports. Values are presented as mean ± SD, except those with parentheses, which are median (interquartile range). Data shown in italics indicate a statistically significant difference. Volume is the volume of tetrastarch or comparator administered. % Transfused is the percentage of patients transfused with allogeneic red cells.

U = units; NR = not reported; MF = modified fluid; HES = hydroxyethyl starch.

[a] MF gelatin also used: group HES 130, 500 (0–4000) mL; group HES 200/0.5, 1700 (0–4000) mL.

[b] Expressed as pure red cell volume (i.e., hematocrit of 100%) rather than blood volume.

[c] Crystalloids also used in the HES 130/0.4 group, 6694±1882 mL.

* $P = 0.019$ versus HES 130/0.4.

was double blinded.[22] These 13 studies were performed in several surgical contexts: minor surgery, cardiac surgery with and without bypass, and major orthopedic and abdominal procedures. Only 1 study concerned pediatric patients.[23] Among these studies, 8 used viscoelastic tests (thromboelastograph, TEG®, Haemonetics, Braintree, MA; or rotational thromboelastometer, ROTEM®, Tem Innovations GmbH, Munich, Germany); 2 used laboratory coagulation variables, 1 flow cytometry, 1 a combination of viscoelastic tests and laboratory coagulation variables, and 1 a combination of viscoelastic tests and flow cytometry. Whatever the coagulation tests assessed, none of these 13 studies reported a higher blood loss associated with the use of tetrastarches. Two studies[22,24] reported that tetrastarch was associated with less perioperative blood loss than with pentastarch. None of the studies reported a difference in packed red blood cell volume transfused between patients treated with the tetrastarch and those treated with the other colloids. One study performed in patients undergoing spine surgery[25] reported a lower incidence of allogeneic blood exposure in patients receiving the tetrastarch compared with those receiving a balanced hetastarch solution. Seven studies[26–32] compared a waxy maize-derived 130/0.4 tetrastarch with pentastarches, hexastarch, hetastarch, modified fluid gelatin, human albumin, and isotonic saline. Of these studies, 5 used viscoelastic tests, 1 laboratory coagulation tests, and 1 flow cytometry. Because none of them reported any results on blood loss and allogeneic blood exposure, the ex vivo coagulation results of effects of these various studied fluids could not be interpreted from a clinical perspective.

Fifteen prospective randomized studies compared 130/0.4 tetrastarch with other fluids to maintain protocol-defined hemodynamic stability. Thirteen studies reported data for perioperative blood loss and 11 for allogeneic blood transfusion (Table 3). Nine trials were double blinded. Surgical procedures included cardiac surgery (with and without cardiopulmonary bypass), major abdominal surgery, and orthopedic surgery. One was performed in children younger than 2 years. In 11 studies, the volume of tetrastarch required to maintain hemodynamic stability was not different than the volume of the control fluid. One study[33] compared the tetrastarch with 20% human albumin, reporting a significantly higher volume of starch required to optimize invasive hemodynamic variables, including cardiac filling pressure and cardiac output. Two studies[34,35] compared the tetrastarch solution with an HBOC, MP4OX, given at a dose of 250 to 500 mL to prevent or to treat hypotension induced by spinal anesthesia. Among these 13 studies, 11 did not report a difference in perioperative blood loss between the groups of patients treated with the tetrastarch and the groups with the control fluid. In the 2 other studies, the use of tetrastarch was associated with significantly less perioperative blood loss when compared with a pentastarch[36] or a 20% human albumin solution.[33] None of the 11 studies presenting data for the volume of packed red blood cells transfused reported a difference between the tetrastarch and the control fluid groups. However, 1 study performed in major orthopedic surgery[37] reported a significantly lower total volume of erythrocytes transfused including allogeneic, autologous, and salvaged red cells in patients treated with the 130/0.4 tetrastarch compared with a hetastarch. Among the 7 studies that presented data on the incidence of allogeneic blood transfusion, 5 reported no difference between the patients treated with the tetrastarch and those treated with the control fluid, whereas 2 reported

Table 2. Studies Using Ex Vivo Coagulation Variables as the Primary Objective and Reporting Blood Loss Data

Authors	Surgery	Starch/comparator	Volume (mL)	No. patients (*n*)	Blood loss (mL)	Volume PRBCs	% Transfused
Chen et al.[70]	Minor	130/0.4	20 mL/kg	20	56±23	NR	NR
		HES 200/0.5	20 mL/kg	20	60±17		
		Ringer lactate solution	20 mL/kg	20	65±19		
Kim et al.[22]	Cardiac	130/0.4	2.4±0.5 L	24	*530±247*	1 (0–4) U	NR
	Off pump	HES 200/0.5	2.3±0.6 L	24	*713±263**	1 (0–3) U	
Mittermayer et al.[28]	Major orthopedic (spine)	130/0.4	6–8 mL/kg/h	19	319 (4–1744)[a]	9 U[b]	3/19
		MF gelatin	8–11 mL/kg/h	21	526 (7–1559)[a]	13 U[b]	8/21
		Ringer lactate solution	13–15 mL/kg/h	21	296 (47–1064)[a]	2 U[b]	1/20
Tiryakioglu et al.[53]	Cardiac	130/0.4	1500	70	430±150	2U[b]	NR
		Ringer acetate solution	1500	70	460±140	2U[b]	
Osthaus et al.[23]	Miscellaneous pediatric	130/0.42	10 mL/kg	25	2.9±4.9 mL/kg/h	NR	NR
		MF gelatin	10 mL/kg	25	4.2±4.6 mL/kg/h		
Schramko et al.[71]	Cardiac	130/0.4	15 mL/kg	15	895 (619–1250)	NR	5/15
		HES 200/0.5	15 mL/kg	15	870 (680–1230)		11/15
		4% albumin	15 mL/kg	15	990 (773–1073		5/15
Schramko et al.[72]	Cardiac	130/0.4	28 mL/kg	15	951±336	15U[b]	NR
		MF gelatin	28 mL/kg	15	1099±420	21U[b]	
		Ringer lactate solution	28 mL/kg	15	921±367	8U[b]	
Muralidhar et al.[24]	Cardiac	130/0.4	1920±230	10	*550±125*	0	0
	Off pump	HES 200/0.5	2200±307	10	*856±131*†	0	0
		MF gelatin	2700±197†	10	*582±159*	0	0
Choi et al.[73]	Cardiac	130/0.4	500	18	471±187[c]	9[c]	7/18[c]
		5% albumin	500	18	573±201[c]	15[c]	11/18[c]
Choi et al.[25]	Major orthopedic (spine)	130/0.4	15 mL/kg	27	1422±688	960±584	*4/27*
		HES 670/0.75	15 mL/kg	27	1373±517	800±289	*12/27*‡
Jin and Yu[74]	Gastric cancer	130/0.4	30 mL/kg	12	349±98	NR	NR
		MF gelatin	30 mL/kg	12	314±58		
		Ringer lactate solution	30 mL/kg	12	321±84		
Liang et al.[75]	Colon cancer	130/0.4	1490±280	18	190±50	0	0
		HES 200/0.5	1510±260	17	210±60	0	0
Zdolsek et al.[45]	Major orthopedic (hip replacement)	130/0.4	1023±188	22	511±228	NR	NR
		130/0.42	886±198	18	539±422		
		HES 200/0.5	952±179	20	595±265		
		Dextran 70	861±230	18	524±200		

Studies for which ex vivo coagulation laboratory data were the primary end point and reported blood loss data. All studies of randomly allocated patients. Author's name in italics indicates publications that specifically indicated that the trial was double blinded. Data shown in italics indicate a statistically significant difference.

MF = modified fluid; NR = not reported; HES = hydroxyethyl starch; PRBC = packed red blood cell.

[a] Expressed as pure red cell volume (i.e., hematocrit of 100%) rather than blood.

[b] Total number of PRBC units transfused in each group.

[c] Corresponds to intraoperative data: postoperative blood loss and erythrocyte transfusion at 8, 16, and 24 hours after surgery were not different between groups.

* $P = 0.016$ versus HES 130/0.4.

† $P < 0.05$ versus HES 130/0.4 and MF gelatin.

‡ $P = 0.03$ versus HES 130/0.4.

a higher incidence of allogeneic blood exposure in patients treated with a pentastarch[38] or the HBOC[35] when compared with those treated with the tetrastarch. In a trial in major abdominal surgery,[39] a significantly lower number of patients randomized to the tetrastarch group were exposed to allogeneic blood products, although perioperative blood losses were not reported. Another study compared 130/0.4 tetrastarch with 5% albumin solution in patients undergoing living donor liver transplantation[40] and did not report blood loss, but the use of packed red blood cells and fresh frozen plasma was not different between the 2 groups.

Two single-blind randomized studies compared the effects of a waxy maize-derived 130/0.4 tetrastarch with either a mixture of colloids or hexastarch and modified fluid gelatin on renal function while presenting data on blood loss and allogeneic blood transfusion[41,42](Table 4). Neither reported a significant difference in perioperative blood loss between the studied colloids.

Finally, 2 single-blind randomized studies compared the effects of a waxy maize-derived 130/0.4 tetrastarch with Ringer's lactate solution and 20% albumin on tissue inflammatory response and organ perfusion in patients undergoing cardiac surgery[43] or hepatectomy[44] (Table 5). In the cardiac study, 1500 mL of either HES 130/0.4 or Ringer's lactate solution was given for cardiopulmonary priming. There were no significant differences in any of the measured variables, including postoperative blood drainage, between the 2 groups, except plasma potassium concentration, which was higher, and plasma chloride concentration, which was lower in the tetrastarch group. In the hepatectomy trial, patients randomized to the colloids required less postoperative fluid volume than those randomized to the

Table 3. Studies Using Hemodynamic Stability as the Primary Objective and Reporting Blood Loss Data

Authors	Surgery	Starch/comparator	Volume (mL)	No. patients (*n*)	Blood loss (mL)	Volume packed red blood cells	% Transfused
Boldt et al.[55]	Cardiac	130/0.4	795±75	10	460±120	3 U[a]	
		HES 200/0.5	820±90	10	550±150	3 U[a]	NR
Gallandat Huet et al.[36]	Cardiac	130/0.4	2550±561	30	*1301±551*	241±419 mL	43
		HES 200/0.5	2466±516	29	*1821±1222**	405±757 mL	48
Langeron et al.[38]	Major orthopedic (expected blood loss >2 L)	130/0.4	1662±641	52	1800 (median)	NR	23
		HES 200/0.5	1696±675	48	2350 (median)	NR	37†
Ickx et al.[49]	Major abdominal	130/0.4	1825±245	20	2000 (600–2800)[&]	0 (0–1) U	5
		HES 200/0.5	1925±183	20	2200 (500–18,000)[&]	0 (0–16) U	10
Sander et al.[76]	Major abdominal	130/0.4	1224±544	29	NS[b]	NS[b]	NS[b]
		HES 200/0.5	1389±610	27	NS[b]	NS [b]	NS[b]
Jungheinrich et al.[77]	Major orthopedic (expected blood loss >2 L)	130/0.4	2035±446	26	1389±694	160±269[c]	
		HES 200/0.5	2000±424µ	26	1621±742	308±549[c]	NR
Gandhi et al.[37]	Major orthopedic	130/0.4	1613±778	49	1.72±1.09 mL/kg	10.1±7.4&	16&
		HES 670/0.75	1584±958	51	1.92±2.11 mL/kg	14.2±9.7&	13&
Mehta et al.[78]	Cardiac Off pump	130/0.4	up to 20 mL/kg	20	295±122	NR	NR
		HES 200/0.5		20	34±150		
Yap et al.[79]	Cardiac	130/0.4	500	20	507±183	NR	NR
		Modified fluid gelatin	500	20	561±227		
Standl et al.[80]	Noncardiac pediatric	130/0.4	113±77[d]	41	96±143	NS[e]	NR
		5% albumin	114±84[d]	41	145±291		
Kim[33]	Major noncardiac	130/0.4	1369±460	41	*324±444*	0.94 U	NR
		20% albumin	883±588*	19	*552±537*‡	1.23 U[f]	
Olofsson et al.[35]	Major orthopedic (hip)	130/0.4	250–500	184	655 (450–1100)	2.5±1.2 U	27
		Oxygenated polyethylene glycol-modified hemoglobin	250–500	183	700 (500–1062)	2.4±1.4 U	38$
Van der Linden et al.[34]	Major orthopedic (hip)	130/0.4	250–500	203	869±446	2.0±0.9 U	36
		Oxygenated polyethylene glycol-modified hemoglobin	250–500	202	953±594	2.2±1.1 U	39

Studies using hemodynamic stability as the primary objective and reporting blood loss data. All studies of randomly allocated patients. Author's name in italics indicates publications that specifically indicated that the trial was double blinded. Data shown in italics indicate a statistically significant difference.

NR = not reported; HES = hydroxyethyl starch.

[a] Total number of packed red blood cells transfused in each group. & corresponds to intraoperative data; postoperative blood loss and erythrocyte transfusion were not different between groups.

[b] From the text written in the Results section.

[c] Cumulative volume up to first postoperative day.

[d] Corresponds to volume administered from baseline to 4–6 hours after surgery. Volume of colloid administered thereafter up to postoperative day 1 was 8±28 mL in the HES 130/0.4 group and 14±30 mL in the albumin group.

[e] Data not presented, statement written in the Abstract.

[f] Mean value calculated from data presented: difference between groups stated significant in the text.

µ, cumulative volume up to first postoperative day.

* $P = 0.05$ versus HES 130/0.4.

† $P = 0.042$ versus HES 130/0.4.

‡ $P < 0.05$ versus HES 130/0.4.

$ $P =$ 0.034 versus HES 130/0.4.

crystalloid. Intraoperative blood loss did not differ among the 3 groups. Postoperative blood loss was not reported, but the authors stated that the use of blood products was not different among groups. Hepatic enzymes increased in all groups but were not different among groups. Postoperative inflammatory reaction assessed by C-reactive protein appeared to be less pronounced in the tetrastarch group.

In summary, 38 studies have evaluated the effects of tetrastarch on blood loss in patients undergoing various surgical procedures, mainly cardiac, major abdominal, or orthopedic surgery. Among these studies, 1602 patients received a tetrastarch solution and 1678 another colloid or crystalloid solution. Among these 38 trials, 36 evaluated the waxy maize-derived 130/0.4 tetrastarch, 1 evaluated the potato-derived 130/0.42 tetrastarch,[23] and 1 evaluated both tetrastarches.[45] The studies varied markedly in their protocol, design, and objectives. Overall, no study demonstrated an increase in perioperative blood loss, allogeneic blood volume transfused, or exposure to allogeneic blood products in patients receiving tetrastarches compared with those receiving other colloids or crystalloids. The ratio of blood loss in the tetrastarch group to other groups varied from 0.75 to 1.01, with a mean and 95% CIs that were < 1.0 for comparison with other HES or human serum albumin, and inclusive of 1.0 for gelatin and crystalloid (Fig. 3). Twenty trials reported on red cell transfusion in 2151 patients. Three hundred eight-six of

Table 4. Studies Evaluating Renal Function as the Primary Objective and Reporting Blood Loss Data

Authors	Surgery	Starch/comparator	Volume (mL)	No. patients (*N*)	Blood loss (mL)	Volume packed red blood cells	% Transfused
Harten et al.[42]	Major abdominal	130/0.4	750 (0–1750)	14	400 (0–2000)	NR	NR
		standard care[a]		15	250 (0–750)		
Mahmood et al.[41]	Major vascular	130/0.4	3911±783	21	1650 (1025–2630)	6 (4–8) U	NR
		Hydroxyethyl starch 200/0.62	3443±1769	21	1500 (1055–2050)	7 (5–10)	
		Modified fluid gelatin	4490±1499	20	1700 (800–3150)	7 (5–10)	

NR = not reported.
[a] Not defined in the publication.

Table 5. Studies Evaluating Systemic Inflammation or Organ Perfusion as the Primary Objective and Reporting Blood Loss Data

Authors	Surgery	Starch/comparator	Volume (mL)	No. patients (*N*)	Blood loss (mL)	Volume packed red blood cells	% Transfused
Shahbazi Sh et al.[43]	Cardiac	130/0.4	1500	35	935±591	NR	NR
		Ringer lactate solution	1500	35	853±553		
Yang et al.[44]	Hepatectomy	130/0.4	3500[b]	30	NR[a]	NS	NR
		20% albumin	800[b]	30		NS	NR
		Ringer lactate solution	10,724±774	30		NS	NR

NR = not reported; HES = hydroxyethyl starch.
[a] Reported intraoperative blood loss was before randomization; no reported blood loss after randomization.
[b] Postoperative crystalloid volume: HES 130/0.4, 6734±393 mL; albumin, 9410±255 mL.

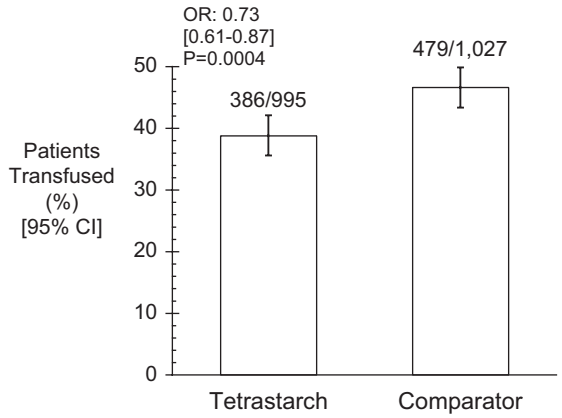

Figure 4. Fraction of patients transfused with allogeneic red cells comparing those given a tetrastarch versus all other comparators. Twenty trials reported allogeneic red cell transfusion (2151 patients); 2 reported no difference without actual data; 18 studies provided data for 2022 patients. Bars are 95% confidence intervals.

995 patients given a tetrastarch received allogeneic red cell transfusion compared with 479 of 1027 given a comparator (OR, 0.73 [0.61–0.87]; $P = 0.0004$; Fig. 4).

Coagulation, Trauma

Two studies reported data on blood loss or transfusion requirements in trauma patients.[46,47] The first study was a single-center randomized single-blind trial that evaluated the effects of repetitive doses of up to 70 mL/kg of HES 130/0.4 compared with pentastarch plus albumin in intensive care unit patients with severe head injury.[47] Blood drainage and estimated other blood loss were not different between the 2 groups of patients. Intracranial bleeding complications were not different between groups (5/16 in the tetrastarch group and 5/15 in the pentastarch + albumin group) and were not accompanied by coagulation disorders. The second study was a single-center randomized double-blind trial comparing HES 130/0.4 with isotonic saline in severely injured patients requiring more than 3 L of fluid resuscitation in which blunt and penetrating trauma were analyzed separately.[46] In the penetrating trauma patients, the volume of erythrocytes transfused was not different between groups (HES 130/0.4, 1553±1562 mL; NaCl 0.9%: 1796±1361 mL). In the blunt trauma patients, the volume of erythrocytes transfused was significantly higher in the tetrastarch group than that in the saline group (HES 130/0.4, 2943±1628 mL; NaCl 0.9%: 1473±1071 mL; $P = 0.005$), as was the volume of transfused fresh frozen plasma and platelet concentrates. These may have been related to a clinically and statistically significant greater severity of injury in the HES group.

Renal

Of the reports meeting the a priori criteria, 41 publications included data regarding renal outcomes of acute renal failure, need for RRT, serum creatinine, creatinine clearance, blood urea nitrogen (BUN), or urine output (Fig. 5). Twenty-six were in major noncardiac surgery, 10 in cardiac surgery, 2 in trauma, 1 in volunteers, and 1 in stroke. Three studies were in children (1 cardiac, 2 noncardiac). The volunteer and stroke studies were excluded from subsequent analysis as they were not in a surgical environment, but neither suggested any renal harm. One additional report examining large infusions of a tetrastarch compared with a pentastarch plus albumin, for up to 28 days in an intensive care unit after head trauma, was not included because there was no specific indication that the patients had undergone surgery.[47] However, there was no suggestion of adverse mortality (no deaths in 16 patients in the tetrastarch group and 2 deaths in 15 patients in the pentastarch group) or adverse renal effects (renal failure: 0 with tetrastarch, 2 with pentastarch, and no differences between groups in serum creatinine or creatinine clearance). This resulted in 38 publications with

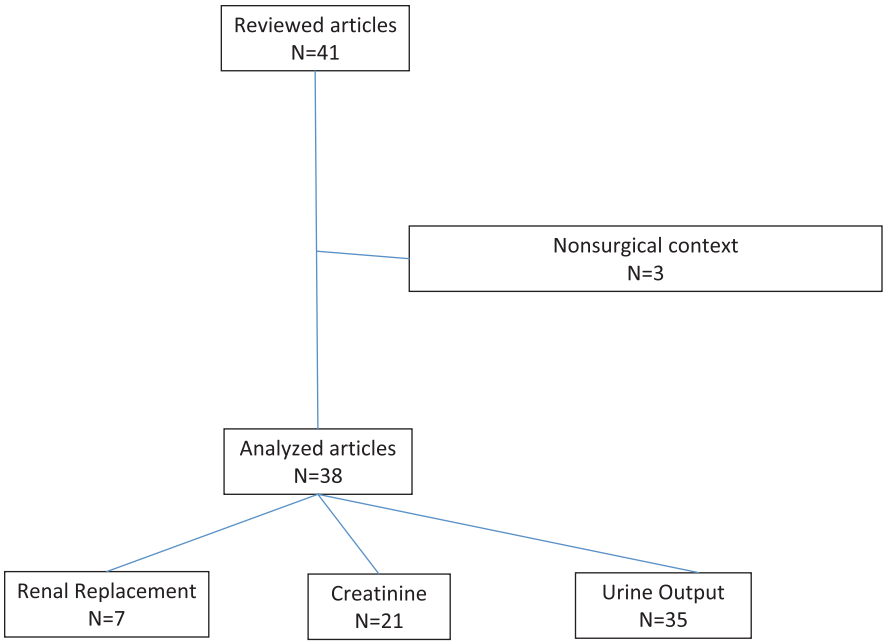

Figure 5. Flow chart of reviewed and analyzed publications related to renal function.

Table 6. Studies Reporting Data for RRT

Author	Patient population	Starch, comparator	Volume (mL)	N (total)	RRT (N)
Godet et al.[51]	Abdominal aortic surgery	HES 130/0.4	2350±1355	32	0
		Gelatin	2136±1174	33	1
James et al.[46]	Trauma (blunt)	HES 130/0.4	6113±1919	20	2
		Saline solution	6295±2197	22	1
	Trauma (penetrating)	HES 130/0.4	*5093±2733*	36	0
		Saline solution	*7473±4321**	31	2
Kasper et al.[54]	Coronary artery bypass	HES 130/0.4	3500 (2000–4500)	59	2
		HES 200/0.5	2500 (1850–3250)	58	3
Lee et al.[69]	Coronary artery bypass	HES 130/0.4	1458±465	53	1
		Crystalloid	8342±1794	53	0
Mahmood et al.[41]	Aortic aneurysm surgery	HES 130/0.4	3911±1783	21	1
		HES 200/0.62	3443±1769	21	1
		Gelatin	4490±1499	20	3
Mukhtar et al.[40]	Liver transplantation	HES 130/0.4	9309±1557	20	1
		Human albumin	8136±2153	20	1
Olofsson et al.[35]	Primary hip arthroplasty	HES 130/0.4	250 or 500	184	0
		MP40X	250 or 500	180	1

Studies reporting data for RRT. All studies randomly allocated patients. Author's name in italics indicates publications that specifically indicated that the trial was double blinded. Data shown in italics indicate a statistically significant difference.
HES = hydroxyethyl starch; RRT = renal replacement therapy.
* $P < 0.05$ versus HES 130/0.4.

3127 randomly allocated patients, of which 1532 were given a tetrastarch and 1595 were given a comparator fluid (Fig. 5).

Renal Replacement Therapy

Seven studies reported the need for RRT (Table 6). Seven of 388 (1.8%) patients receiving a tetrastarch had RRT compared with 12 of 402 (3.0%) receiving a comparator (OR, 0.60 [0.23–1.53]; $P = 0.35$; all were other colloids, except for 1 group of crystalloid in 1 trial).[46]

Creatinine

Twenty-one studies reported on serum creatinine concentrations or creatinine clearance after administration of the test fluids (Table 7). One thousand five patients were given a tetrastarch, and 1051 patients were given a comparator for studies in major abdominal surgery,[42,48–50] abdominal aortic surgery,[41,51] cardiac surgery,[43,52–55] pediatric cardiac surgery,[21] orthopedic surgery,[34,35] major urologic surgery,[39] laparoscopic abdominal surgery,[56] hepatectomy,[44] hepatic transplantation,[40] and renal transplantation.[57] The period for which creatinine was reported varied up to 14 days after administration. All but 3 studies showed no difference in peak creatinine concentrations or nadir creatinine clearances during the postoperative period. Two studies found a statistically better outcome for a tetrastarch,[41,56] and 1 found a lower creatinine with a crystalloid comparator, but no difference in change of creatinine or creatinine clearance.[53] Overall, there was no indication that administration of a tetrastarch resulted in creatinine clearance or plasma concentrations that differed from that of any other group (Fig. 6). The ratio of peak serum creatinine in the tetrastarch group to other groups varied from 0.86 to 1.08, with 95% CIs inclusive of 1.0.

Table 7. Studies Reporting Serum Creatinine or Creatinine Clearance Data

Author	Patient population	Starch, comparator	Volume (mL)	No. patients per group (N)	Creatinine baseline (mg/dL)	Creatinine peak (mg/dL)
Boldt et al.[55]	Cardiac surgery	HES 130/0.4	795±75	10	0.88±0.15	1.01±0.26
		HES 200/0.5	820±90	10	0.91±0.17	1.04±0.22
Fenger-Eriksen et al., 2005[81]	Major spine surgery	HES 130/0.4	4000 (3000–6000)	6	0.83 (0.61–1.01)	0.74 (0.58–0.82)
		Saline	7000 (700–10,000)	5	0.87 (0.57–1.11)	0.81 (0.73–0.85)
Gallandat Huet et al.[36]	Cardiac surgery	HES 130/0.4	2550±561	30	1.10±0.16	1.23±0.20
		HES 200/0.5	2466±516	29	1.12±0.16	1.07±0.23
Godet et al.[51]	Abdominal aortic surgery	HES 130/0.4	2350±1355	32	*1.23±0.33*	1.40±0.70
		Gelatin	2136±1174	33	*1.26 ±0.28*	1.44±0.70
Hanart et al.[21]	Pediatric cardiac surgery	HES 130/0.4	Intraoperative, 50 (45–50)/kg	60	0.32 (0.27–0.39)	0.31 (0.25–0.40)
		Human albumin	Intraoperative, 50 (37–50)/kg	59	0.27 (0.24–0.35)	0.30 (0.23–0.36)
Harten et al.[42]	Emergency abdominal surgery	HES 130/0.4	750 (0–1750)	14	0.97 (0.62–1.82)	0.97 (0.68–1.70)
		"Standard care"		15	1.14 (0.80–2.95)	1.08 (0.68–3.41)
Heinze et al.[39]	Major urological surgery	HES 130/0.42	2540±1232	46	0.85±0.19	0.89±0.19
		HES 200/0.5	2290±1040	47	0.83±0.26	0.86±0.28
Ickx et al.[49]	Major abdominal surgery	HES 130/0.4	1825±245	20	1.05±0.13	0.95±0.19
		HES 200/0.5	1925±183	20	1.15±0.12	1.02±0.12
Jover et al.[56]	Laparoscopic cholecystectomy	HES 130/0.4	500	14	CrCl: 116±28	*CrCl: 176±14*
		Ringer lactate solution	500	15	CrCl: 109.± 21	*CrCl: 62±6.6**
Kasper et al.[82]	Major surgery	HES 130/0.4	500	30	Creatinine: normal; no significant change	Creatinine: normal; no significant change
		HES 200/0.5	500	30		
Kasper et al.[54]	Coronary artery bypass	HES 130/0.4	3500 (2000–4500)	59	0.9±0.2	1.0±0.3
		HES 200/0.5	2500 (1850- 3250)	58	0.9±0.2	1.1±0.4
Kim et al.[22]	Coronary artery bypass surgery	HES 130/0.4	2400±500	24	0.96±0.2	1.0±0.2
		HES 200/0.5	2300±600	24	1.0±0.2	0.9±0.2
Mahmood et al.[41]	Aortic aneurysm surgery	HES 130/0.4	3911±1783	21	1.1±0.01	*1.0±0.01*
		HES 200/0.62	3443±1769	21	1.2±0.03	1.2±0.1
		Gelatin	4490±1499	20	1.1±0.01	*1.6±0.2**
Mukhtar et al.[40]	Liver transplantation	HES 130/0.4	9309±1557	20	1.1±0.1	1.5±0.3
		Human albumin	8136±2153	20	1.1±0.3	1.3±0.4
Olofsson et al.[35]	Primary hip arthroplasty	HES 130/0.4	250 or 500	184	CrCl: 82 (62–100) mL/min	CrCl: 96 (78–122) mL/min
		MP4OX	250 or 500	180	CrCl: 82 (70–100) mL/min	CrCl: 94 (72–114) mL/min
Shabazi et al.[43]	Cardiopulmonary bypass	HES 130/0.4	1500	35	0.96±0.18	1.25±0.35
		Ringer lactate solution	1500	35	1±0.15	1.21±0.45
Tiryakioglu et al.[53]	Cardiopulmonary bypass priming	HES 130/0.4	1500	70	1.1±0.1	*1.4±0.24*
		Ringer lactate solution	1500	70	1.0±0.2	*1.1±0.22**
Van der Linden et al.[52]	Cardiac surgery	HES 130/0.4	48.8±20.9/kg	65	1.05±0.23	1.02±0.29
		Gelatin	48.9±19.3/kg	68	1.09±0.29	1.17±0.74
Van der Linden et al.[34]	Primary hip arthroplasty	HES 130/0.4	250 or 500	201	CrCl: no differences between groups	CrCl: no differences between groups
		MP4OX	250 or 500	198		
Wu et al.[57]	Living-related kidney transplantation	HES 130/0.4	1107±308	38	8.17±2.47	0.86±0.23
		Gelatin	1178±320	39	8.27±2.42	1.03±0.41
Yang et al.[44]	Hepatectomy	HES 130/0.4	4500 + crystalloid	26	Normal, no significant differences between groups	Normal, no significant differences between groups
		Human albumin	1800 + crystalloid	30		
		Ringer lactate solution	12,924	25		
Yap et al.[79]	Coronary artery bypass surgery	HES 130/0.4	500	21		1.09±0.25
		Gelatin	500	21		1.35±0.57

Studies reporting serum creatinine or creatinine clearance data. All studies of randomly allocated patients. Author's name in italics indicates publications that specifically indicated that the trial was double blinded. Data shown in italics indicate a statistically significant difference.

In addition to the data presented, 2 additional studies[34,35] did not report serum creatinine concentrations but did show creatinine clearance data: there were no differences between HES 130/0.4 and MP4OX or any differences in the incidence of creatinine concentrations >0.3 mg/dL or ≥1.5× baseline versus the comparator. Sample sizes were 184 and 180 for HES and 201 and 198 for the comparators, respectively.

CrCl = creatinine clearance; HES = hydroxyethyl starch.

*$P < 0.05$ versus HES 130/0.4.

Of special interest is renal function where the risk of renal impairment is increased: after kidney or hepatic transplantation or abdominal aortic surgery. In a trial of 80 patients undergoing renal transplantation, 40 were randomly allocated to receive a tetrastarch and 40 were given 4% succinylated gelatin,[57] with volumes of colloid and red cells administered and operative duration that did not differ between the groups. After transplantation, serum creatinine, serum β2 microglobulin, urinary β2 microglobulin, and α1 microgloblulin concentration decreased similarly in the 2 groups, but BUN decreased more rapidly and urinary microalbumin reached a statistically lower concentration in the tetrastarch group than that in the gelatin group. In a trial of 40 patients undergoing hepatic transplantation, 20

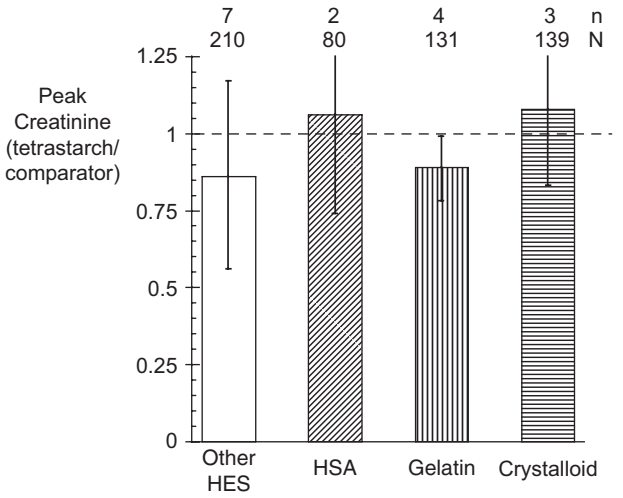

Figure 6. Ratio of peak postoperative serum creatinine concentration for patients given a tetrastarch to the peak postoperative serum creatinine for patients given comparators. The bars are mean values (with 95% confidence intervals) of the mean or median group data reported in all publications providing serum creatinine data. *n* = number of publications providing data; *N* = number of patients in those trials who were given a tetrastarch; HSA = human serum albumin. No statistical analyses were performed.

patients were randomly allocated to receive either a tetrastarch or a human serum albumin.[40] There were no significant differences for serum creatinine or creatinine clearance between the 2 groups. A study of 65 patients (random allocation: 32 given a tetrastarch, 33 given gelatin) with preoperative renal impairment who underwent abdominal aortic surgery found no differences between the 2 groups for postoperative serum creatinine, creatinine clearance, or urine output.[51] Another study randomly allocated 21 patients to be given a tetrastarch, 21 patients to be given a pentastarch, and 20 patients to be given gelatin during aortic aneurysm surgery.[41] Urinary α1 microglobulin, immunoglobulin G:creatinine ratio, BUN, and creatinine were lower in the tetrastarch group than that in the gelatin group.

Urine Output

Thirty-five trials with 2616 patients compared urine output after random allocation to receive a tetrastarch (1264 patients) or a comparator (1352). No study reported a statistical difference between groups. Although some trials had a relatively small sample size, none of the reported values were of sufficient magnitude to suggest that larger studies would detect a difference that might be clinically meaningful.

In summary, 24 trials evaluated the need for RRT or creatinine clearance or concentration in 1134 patients given a tetrastarch and 1177 given a comparator. There was no evidence that tetrastarch administration induced renal impairment as judged by these variables, including in subpopulations of patients at high risk for postoperative degradation of renal function.

DISCUSSION

We found that trials randomly allocating patients to receive tetrastarch just before or during surgery, or both, do not appear to indicate that tetrastarch is associated with the adverse clinical outcomes of increased blood loss, increased use of allogeneic red cells, increased incidence of renal impairment or failure, or mortality. The data failed to provide any suggestion of such adverse consequences of tetrastarch administration in the surgical environment. We assessed only trials that randomly allocated patients to receive the tetrastarch or the comparator to minimize bias, but we did evaluate both blinded and unblinded trials. Although an unblinded trial is vulnerable to greater bias compared with a blinded trial, we did not detect any difference in the results of these 2 types of studies.

A previous examination[58] reviewed individual data of patients from 7 studies comparing HES 130/0.4 to HES 200/0.5 for perioperative intravascular volume replacement. Although patients randomized to the tetrastarch group received more starch than those randomized to receive pentastarch, they had less perioperative blood loss, were less frequently exposed to allogeneic blood products, and when transfused received a smaller volume of packed red blood cells.

It is worth noting that the duration of follow-up in the trials that we evaluated was relatively short. It is understandable that the follow-up period was limited, as most of the trials were performed before any suspicion was raised of possible long-term adverse effects. Furthermore, many of the trials examined were for regulatory purposes, and their design was driven by regulatory considerations. The relatively limited duration of reporting, in part, may account for the difference between our results of no adverse safety effects and the opposite finding of other reports, such as the recently completed so-called 6S study.[13] In that trial, follow-up was for 90 days, but no differences in survival were noted until 60 days after HES administration. In addition to the issue of reporting duration and study design (a randomized clinical trial versus review of previously published studies), other important differences, such as the long-term use of large volumes of HES, likely contributed to the differing results. Patient population is perhaps the most important difference between the studies that we analyzed and the 6S trial. It is likely that the preponderance of patients we included had relatively normal, intact endovascular function and glycocalyces; the opposite is likely to have been the case in the septic shock patients studied in the 6S trial (only 45 of the 798 patients were not in septic shock at the time of enrollment, and there was no suggestion of an adverse outcome in that small subpopulation). The endovascular glycocalyx acts as a selective barrier for exchange of fluid and molecules between plasma as tissue spaces,[59–61] and its degradation results in immediate tissue edema.[61] Septic shock and hypoxia degrade endovascular integrity and the glycocalyx,[16,62] resulting in the extravasation of large molecules and fluid from intravascular to extravascular spaces. Such substantial extravasation of HES, together with an increased need for volume augmentation, would have resulted in the loss of its intravascular colloidal function, creating a need for additional fluid therapy, and unknown consequences for abnormal amounts of extravascular HES, either or both of which could have contributed to the observed increased late mortality in the 6S trial.

A recent meta-analysis assessed 25 trials of either perioperative or acutely ill patients, attempting to discern the influence of retracted publications, apparently as a prelude to the CHEST.[18] Six of the trials were in intensive

care units, and 3 of those trials were in severe sepsis encompassing 101 patients of the total 1608 reviewed. We assessed considerably more trials strictly in the surgical setting, with more than 3 times as many patients. Thus, the 2 reviews differ in scope and intent.

It should be further noted that none of the trials we examined, except the 2 trials with an HBOC,[34,35] had a substantial number of patients, thus limiting the power of any one individual study. However, examination of the 38 surgical trials that reported blood loss in 1602 patients treated with tetrastarch and compared with 1678 patients given a comparator and 1134 patients given a tetrastarch and compared with 1177 patients given a comparator in 24 trials in whom renal function (RRT or creatinine) was examined did not provide a hint of increased blood loss, decreased renal function, or mortality. In fact, in those trials in which the comparator fluid was either other starches or human serum albumin, the blood loss with the tetrastarches was 0.88 and 0.75 of those comparators, respectively, with 95% CIs that did not cross 1.0. In addition, the 18 trials of 2022 patients reporting data for numbers of patients transfused with allogeneic red cells (not including the 2 trials that reported "no difference" without presenting data) suggest the possibility of a lesser transfusion rate with a tetrastarch than the comparators.

Of further consideration is the reliability of the primary clinical end point we assessed for coagulation function: that of blood loss. The estimation of intraoperative blood loss is subject to interperson variability,[63] and those values frequently differ from those estimated from changes in hematocrit.[64] While the absolute values reported in the clinical trials we assessed might have inaccuracies, the relative values comparing tetrastarches to other fluids administered should be more reliable, as within a trial the blood losses were estimated in the same manner by the same personnel.

Only 1 study in blunt trauma patients reported a higher exposure to blood product in patients treated with HES 130/0.4 compared with those treated with NaCl 0.9%.[46] In blunt trauma patients where there is more diffuse microvascular damage, adverse effects on coagulation may lead to greater blood loss and higher exposure to blood products. However, the authors (and we) could not form a conclusion regarding the influence of HES 130/0.4 on coagulopathy and bleeding in the blunt trauma patients as that particular group had a higher injury severity and the worst coagulation screen on admission, perhaps reflecting a higher incidence or severity of trauma-induced coagulopathy.[19]

We had decided, before analyzing the reports, not to perform a formal meta-analysis because we judged from our knowledge that the trials were too heterogeneous in design and populations studied. We did not examine the use other HES products (pentastarches and hetastarches) for use in surgery or the use of tetrastarches during other circumstances (e.g., sepsis), and thus our conclusions apply only to tetrastarches when used in the surgical setting.

In summary, we conclude that data in the peer-reviewed literature do not suggest an adverse safety signal when tetrastarches are used intraoperatively or in the immediate postoperative period or both. We did not address the continued postoperative use, as is being performed in the CHEST trial; thus, the data set we have presented here will stand separately from whatever those findings will be. The limitations (such as duration of follow-up) of the underlying data we examined suggest that it may be worthwhile to gather additional data in the postoperative period. On the basis of our inability to detect a hint of an adverse signal, at this time it would seem an inappropriate use of resources to conduct a full-scale randomized controlled trial. Rather, as hypothesis generating, it could be useful to examine existing databases or generate data in registries.

Appendix 1

The electronic search strategies that we used were based on the following keywords: Hydroxyethyl starch, HES 130, Tetrastarch, Voluven, Venofundin, Plasmavolume redibag, Vitafusal, VitaHES, and Volulyte.

Search strategies for each electronic database are detailed as follows:

CENTRAL: (HES 130) or (voluven) or (volulyte) or (hydroxyethyl starch) or (tetrastarch) or (Volulyte) or (Venofundin) or (Tetraspan) or (PlasmaVolume Redibag) or (Vitafusal) or (VitaHES) in Cochrane Reviews, Other Reviews and Clinical Trials

MEDLINE 1997–present (OVID)

1 randomized controlled trial.pt.
2 controlled clinical trial.pt.
3 randomized.ab.
4 placebo.ab.
5 clinical trials as topic.sh.
6 randomly.ab.
7 trial.ti.
8 or/1–7
9 exp animals/ not humans.sh.
10 8 not 9
11 Hetastarch/
12 hydroxyethyl.mp.
13 starch.mp.
14 12 and 13
15 tetrastarch.mp.
16 voluven.mp.
17 hes.mp.
18 "130".mp.
19 17 and 18
20 volulyte.mp.
21 venofundin.mp.
22 vitaHES.mp.
23 tetraspan.mp.
24 plasmavolume redibag.mp.
25 11 or 14 or 15 or 16 or 19 or 21 or 23
26 10 and 25

EMBASE 1997–present

1 hes.mp.
2 "130".mp.
3 1 and 2
4 hydroxyethyl.mp.
5 starch.mp.
6 4 and 5
7 plasmavolume.mp.
8 redibag.mp.
9 7 and 8
10 (Voluven or tetrastarch or volulyte or venofundin or tetraspan or vitafusal or vitaHES).mp.
11 hetastarch.mp. or hetastarch/
12 3 or 6 or 9 or 10 or 11
13 (random or cross?over or factoral$ or placebo$ or volunteer$).mp.
14 ([singl$ or doubl$ or trebl$ or tripl$] adj3 [blind$ or mask$]).mp.
15 13 or 14
16 (animal not [human and animal]).sh.
17 15 not 16

Appendix 2

Publications known to the authors but not retrieved by the electronic search:

1. Shahbazi S et al.: Iran Cardiovasc Res J 2011; 5: 24–31
2. Kim JY et al.: Korean J Anesthesiol 2007; 53: S14–21
3. Kim DH: Anesth Pain Med 2009; 4: 235–214
4. Heinze H et al.: Applied Cardiopulmonary Pathophysiology 2009: 13: 11–19
5. Fenger-Eriksen C et al.: Acta Anaesthesiol Scand 2005; 49: 969–974

Appendix 3

Brand Names of Various HES Products
670/0.75: Hextend
600/0.75: Hespan
250 or 262/0.45: Pentaspan
200/0.5: Hemohes
200/0.62: Hyperhes
130/0.4: Voluven
130/0.42: Tetraspan; Venofundin

DISCLOSURES:

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Contribution: This author helped design the research, review the articles, review the data, and write the manuscript.
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Name: Michael James, MB ChB, PhD, FRCA, FCA(SA).
Contribution: This author helped design the research, review the articles, review the data, and write the manuscript.
Attestation: Michael James attests to the integrity of the analysis and approved the final manuscript.
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Name: Michael Mythen, MD, FRCA.
Contribution: This author helped design the research, review the articles, review the data, and write the manuscript.
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Name: Richard B. Weiskopf, MD.
Contribution: This author helped design the research, review the articles, review the data, and write the manuscript.
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This manuscript was handled by: Jerrold H. Levy, MD, FAHA.

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