Hydroxyethyl Starch 130/0.4 and Its Impact on Perioperative Outcome: A Propensity Score Matched Controlled Observation Study

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BACKGROUND: Adverse effects of hydroxyethyl starches (HESs) have been verified in patients suffering from sepsis or kidney disease, but not in surgical patients at large. The investigation aimed to determine whether the use of HES 130/0.4 was associated with the incidence of acute postinterventional adverse events compared to Ringer's acetate alone in a perioperative setting.

METHODS: This propensity score matched, controlled observational study was performed in a single-centre university hospital. The perioperative data of 9085 patients were analyzed. Group matching was based on 13 categories including demographic data, type of procedure, and 5 preexisting comorbidities. Duration of procedure and intraoperative transfusion requirements were integrated in the matching process to reduce selection and indication bias. The primary outcome was incidence of postoperative kidney failure. Secondary outcomes were in-hospital mortality, fluid requirements, blood loss, hemodynamic stability, and the need for postoperative intensive care unit (ICU) treatment.

RESULTS: The administration of HES 130/0.4 was not associated with an increased frequency of postoperative kidney failure. In-hospital mortality (Ringer's acetate: 2.58%; HES 130/0.4: 2.68%) and the need for ICU care (Ringer's acetate: 30.5%; HES 130/0.4: 34.3%) did not differ significantly between groups. Significant intergroup differences were observed for mean blood loss (Ringer's acetate: 406 ± 821 mL; HES 130/0.4: 867 ± 1275 mL; $P < .001$) and median length of hospital stay (Ringer's acetate: 10.5 (5/17) days; HES 130/0.4: 12.0 (8/19) days; $P < .001$).

CONCLUSIONS: An association between intraoperative HES therapy and postoperative kidney failure was not observed in a mixed cohort of elective surgical patients. In addition, HES 130/0.4 was not associated with an increased morbidity or the need for ICU therapy in this propensity score matched study. (Anesth Analg 2018;126:1949–56)

KEY POINTS

- **Question:** Does the administration of hydroxyethyl starch (HES) 130/0.4 increase the frequency of postoperative kidney failure in a perioperative setting?
- **Findings:** In a large propensity score matched cohort with Ringer's acetate as a comparator, the use of HES 130/0.4 was not related to postoperative kidney failure.
- **Meaning:** Perioperative therapy with HES 130/0.4 has no association to kidney failure, when administered in a mixed cohort of elective surgical patients.

Since their introduction in the 1970s, hydroxyethyl starches (HESs) have found widespread uses in perioperative and critical care medicine. Perioperatively their administration has been associated with reduced fluid requirements, increased tissue oxygen tension, and better hemodynamic stability. However, especially in the past decade, there has been an intensive debate concerning the safety of HES preparations. A number of studies in critically

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ill patients have suggested that the use of HES might have detrimental effects on kidney function in patients with severe sepsis and/or renal disease.[1–3] Though the methodological quality and the results of these studies have been extensively discussed, there was sufficiently compelling evidence against using HES in intensive care medicine for the European Medicines Agency (EMA) to recommend revoking their approval (EMA, 640658) in June 2013.[4]

Though adverse effects of HES have been clearly verified in intensive care unit (ICU) patients, they have not been established in surgical patients at large.[5–7] Thus, the limitations concerning the perioperative use of HES have been partially revised by some national expert committees.[8]

While acute kidney injury occurs frequently in intensive care medicine, the incidence has been put at below 5% in patients scheduled for low- to medium-risk surgery.[9] As a consequence, very large randomized controlled trials would be necessary to detect adverse effects of HESs on renal function in a routine perioperative setting, which, to date, have not been forthcoming. High-quality propensity score matching can mimic randomization to some extent and, when generated out of retrospective cohort analyses, is able to provide large numbers of patients.[10] In addition, a propensity score matched cohort analysis can be controlled rather effectively with respect to patient population uniformity, confounders, and variables of interest.[5–7] We conducted a large-scale investigation of surgical patients who had received either Ringer's acetate (RA) alone or in combination with HES 130/0.4 (hydroxyethyl starch, molecular weight 130 kDa; degree of substitution 0.4, waxy maize-based). Propensity score group matching was performed to adjust for known confounders and to reduce bias. We hypothesized that there would be an association between the use of HES 130/0.4 and postoperative kidney failure.

METHODS

Data Generation and Subject Selection

After approval by the Ethics Committee of the University of Munich, we accessed the software used to generate our department's electronic anesthesia records (NarkoData, IMESO GmbH, Giessen, Germany). This software is based on a database collecting anesthesia-relevant perioperative data for all patients undergoing anesthesia. Second, the hospital's patient data management system (KAS, SAP Deutschland SE & Co. KG, Walldorf, Germany) was accessed. It captures administrative data such as length of hospital stay (LOSH) and some medical information such as patient's comorbidities. Finally, the hospital's laboratory database was used to retrieve perioperative laboratory values. Using these 3 databases, a set of parameters was generated which, on the one hand, enabled a propensity score matching process and, on the other hand, provided a set of defined outcome variables. Informed consent was waived because patient data were irreversibly anonymized before extraction (Clinical Trial Number: UE 102–14). This manuscript adheres to the applicable Enhancing the QUAlity and Transparency Of health Research (EQUATOR) guidelines.

Data deriving from surgical procedures were analyzed to compare 2 groups of patients who either received RA alone (Jonosteril, Fresenius Kabi, Bad Homburg, Germany) (group RA) or a combination of RA with HES 130/0.4 (Voluven, Fresenius Kabi, Bad Homburg, Germany) (group RA-HES). A similar comparison, which is demonstrated in Supplemental Digital Content 1, Appendix 1, http://links.lww.com/AA/C194, was performed between RA and a 20% albumin solution (Human-Albumin 20% Behring, CSL Behring GmbH, Marburg, Germany) (group RA-Alb).

To initiate this retrospective analysis, all adult patients undergoing surgical or diagnostical procedures requiring anesthesia during a 6-month period were evaluated. Part 1 of this 6-month period took place from August 1, 2012 to October 31, 2012. Part 2 was from August 1, 2013 to October 31, 2013, when HES 130/0.4 was not used at the authors' institution due to the restrictions imposed by the EMA in June 2013.[4] Thus, patients who had received HES 130/0.4 derived solely from the 2012 period. Patients in group RA were enrolled in both periods. The temporal subdivision of data sampling was necessary to gather a sufficient number of patients for group RA who matched patients of group RA-HES in terms of comorbidities, as well as course and type of surgery. This could not be achieved exclusively in 2012 when HES 130/0.4 was available. In patients who underwent more than 1 surgery, only the first procedure was included in the analysis and the observation period was finished at the time of the second procedure.

Second, patients undergoing diagnostic procedures and surgical procedures without a relevant risk of bleeding (for example ophthalmologic surgery) who had no indication for colloid use, as well as those with datasets lacking an exact procedure specification, were excluded from the analysis (Figure).[11]

Finally, from this cohort, 2 subgroups were established: Subgroup 1 consisted exclusively of patients undergoing major surgery, implicating a high risk of significant bleeding. This subgroup was created from the whole cohort before any matching and its study groups (RA; RA-HES) were subsequently matched separately (Figure).

Subgroup 2 was built out of the whole cohort after propensity score matching and consisted of patients in whom the RIFLE criteria could be applied. The RIFLE criteria (an acronym indicating Risk of renal failure, Injury to the kidney, Failure of kidney function, Loss of kidney function, and End-stage renal failure) are a diagnostic means to evaluate changes in postprocedural kidney function put forward by the Acute Dialysis Quality Initiative group in 2004.[12] They are based on a calculated ratio of pre-and postprocedural creatinine values, among other parameters. The serum creatinine cutoff values characterizing the RIFLE classes are given in Supplemental Digital Content 2, Table A2/1 in Appendix 2, http://links.lww.com/AA/C195.[12–14]

After propensity score matching, group-wise comparisons were performed according to the Figure. Our hypothesis, statistical analysis plan, and primary and secondary outcomes were clearly defined before data interrogation.

The primary outcome was frequency of acute postoperative kidney failure (pAKF). pAKF was defined as a patient needing any kind of postprocedural renal replacement therapy (RRT) for the first time in his or her patient career.

Secondary outcome parameter was the in-hospital mortality after surgery. Patients who were discharged from the hospital were considered survivors and the mortality rates of patients transferred to other hospitals

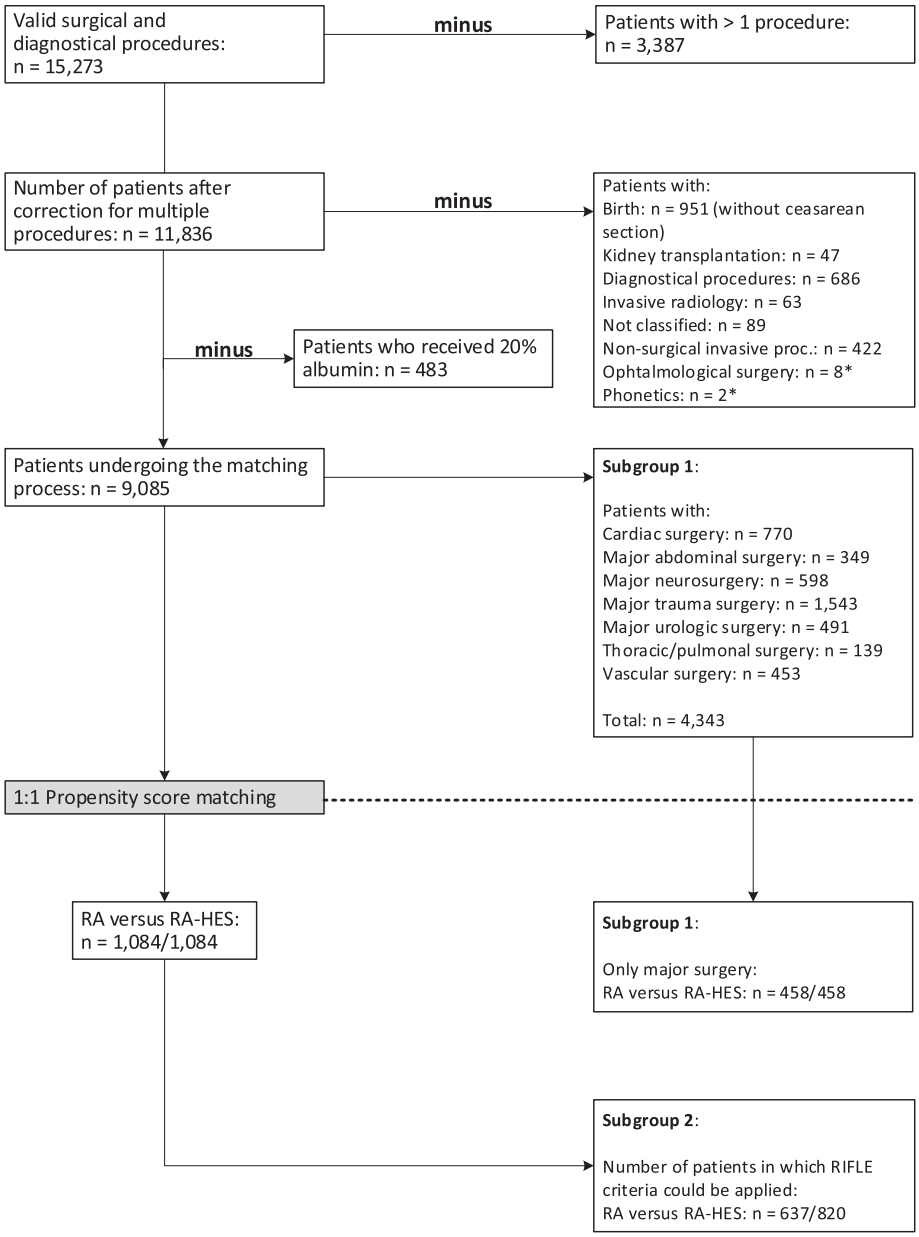

Figure. Flow chart of patient selection. HES indicates hydroxyethyl starch 130/0.4; RA, Ringer's acetate; RIFLE, Risk of renal failure, Injury to the kidney, Failure of kidney function, Loss of kidney function, and End-stage renal failure.

*: The anesthesia documentation software, needed for data gathering was first installed at the end of the observation period in the respective clinics. Therefore, the number of cases is low.

were not evaluated. Further secondary outcomes were intraoperative fluid requirements (crystalloids and colloids), platelet, fresh frozen plasma requirements, mean blood loss, mean arterial pressure (MAP), and mean heart rate. LOSH and the necessity for ICU admission were also investigated. In subgroup 1, the same primary and secondary outcomes as for the whole cohort were evaluated.

In subgroup 2, the RIFLE criteria could be applied because both pre- and postoperative creatinine values were available (Figure).[13] The post/preoperative creatinine ratios were calculated and regarded as a secondary outcome parameter. If more than 1 preoperative creatinine value was available, the latest preoperative value was used. If more than 1 postoperative value was known, the maximum creatinine value until the 90th postoperative day was used. Because the duration of postoperative serum creatinine monitoring was not controlled, the RIFLE criteria of "Loss" and "End-stage renal disease" could not be applied.[14]

During the study, intraoperative fluid therapy was administered according to well-defined standard operating procedures (SOPs), which are given in Supplemental Digital Content 2, Table A2/2 in Appendix 2, http://links.lww.com/AA/C195.[15–18] The appropriate application of these SOPs by duty anesthetists was trained in repeated department-wide teaching sessions and was controlled by supervising senior physicians.

Statistical Analysis

For all data analyses, SPSS version 23 (IBM Corporation, Armonk, NY), Microsoft Excel 2016 (Microsoft Corporation, Redmond, WA), and the free software package "R," version 3.3.1 including the "Matchit" and the "ROC" plugin, were used. The existence of a Gaussian distribution of data was evaluated using the Kolmogorov-Smirnov test; to test for equal variances, the *F* test was applied. Skewed data are displayed as median ± interquartile range, otherwise they are given as mean ± standardized deviation of the mean.

To account for potential confounders between study groups, each patient who was given both crystalloids and HES (group RA-HES) was matched to a control patient who was given only RA (group RA) across 13 different variables: gender, age, body mass index, physical status according to the American Society of Anaesthesiologists classification system, duration of surgery, type of surgical procedure, the number of packed red blood cells (PRBCs) transfused, maximal intraoperative noradrenaline requirements, and up to 5 preexisting comorbidities. Procedure type was classified according to the German OPS catalog version 2016, whereby codes were combined into 24 main categories.[19] Comorbidities were classified according to International Classification of Diseases (ICD-10) catalog.[20] Comorbidities were combined into 17 main categories according to the Charlson comorbidity index using the algorithms of Deyo and Quan (Supplemental Digital Content 2, Table A2/3 in Appendix 2, http://links.lww.com/AA/C195).[21–23] Intraoperative PRBC transfusion and noradrenaline requirements are known to directly influence pAKF.[24] Independently of this fact they merited inclusion into the matching process because alongside length of surgery, these parameters are important markers of the severity of the surgical pathology and the complexity of the intraoperative course, which in our point of view may be a further important "confounding factor." On the other hand, intraoperative blood loss was not included because duty anesthetists can only roughly estimate it. MAP is known to affect renal function, but it in turn is influenced by the nature of fluid therapy and was therefore interpreted as being an outcome parameter. To obtain the best matching results, ie, to compare only patients who shared a maximum of similarities, the "nearest neighbor method" was applied and a strict 1:1 ratio was maintained with regard to the 2 study groups. After matching, the Mann-Whitney *U* test was used for group comparisons when data were not normally distributed; otherwise a Student *t* test or Welch test was applied. Associations regarding categorical demographic and outcome variables were assessed using Pearson χ^2 test or Fisher exact test where necessary. Concerning the primary outcome parameter, the odds ratio, its 95% confidence interval (CI), and the corresponding *P* value were calculated. *P* values were used as a measure of overall significance. For all comparisons, a value of $P < .05$ was considered significant.

RESULTS

Structure of Retrieved Data and Demographic Analysis

In total, the data of 9085 surgical patients were analyzed. During the matching process, the number of patients was reduced to 2168 for the whole cohort and 916 for subgroup 1, to provide a maximum conformity between the study groups (Figure). Demographic data before and after matching are shown in Table 1. All patient demographic variables were well balanced after matching. Perioperative data contributing to matching are also demonstrated in Table 1. ASA classification and duration of surgery data were well balanced, whereas number of PRBCs transfused and maximum noradrenaline requirement still differed between groups. The distribution of surgical and diagnostic procedures is given in Table 2, showing that some significant differences between groups persisted despite matching. Nevertheless, the frequency of high-risk surgical procedures in group RA increased after matching. The fact that HES 130/0.4 was only administered in surgical procedures accompanied by a relevant blood loss led to a corresponding increase in high-risk surgeries in the RA group. As pointed out above, the frequency of 17 categories of comorbidities was also part of the matching process. After matching, significant differences concerning this item could no longer be noticed between study groups (Supplemental Digital Content 2, Table A2/3 in Appendix 2, http://links.lww.com/AA/C195; $P > .05$ for all group comparisons). Data concerning the quality of the matching procedure are given in Supplemental Digital Content 3, Tables A3/1–A3/8 and Figures A3/1–A3/4 in Appendix 3, http://links.lww.com/AA/C196. Overall, a balance

Table 1. Demographic and Perioperative Data Before and After Matching

		Crystalloid Versus HES After Matching	
	All Before Matching	RA	RA-HES
N (patients)	9085	1084	1084
Age (y)	56 (38/70)	65 (52/74)	65 (49/73)
BMI (kg)	25.5 (22.5/28.4)	25.8 (23.0/29.4)	25.9 (23.4/29.3)
Gender (M/F) (%)	49.0/51.0	47.9/52.1	48.1/51.9
ASA classification	2.0 (2.0/3.0)	3.0 (2.0/3.0)	3.0 (2.0/3.0)
Duration of surgery (min)	68 (34/128)	121 (58/219)	134 (71/204)
PRBC (mL)	32 ± 195	119 ± 386[a]	173 ± 529[a]
Maximum noradrenaline requirements during surgery (mg/h)	0.22 ± 0.40	0.52 ± 0.71[b]	0.65 ± 2.32[b]

Skewed data are given as median (25th/75th percentile), normally distributed data as mean ± standardized deviation of the mean, and as proportions (gender). Mann-Whitney *U* test for skewed data; Student *t* test for normally distributed data; Pearson χ^2 test for proportions.

Abbreviations: ASA, American Society of Anesthesiologists; BMI, body mass index; RA, Ringer's acetate; HES, hydroxyethyl starch 130/0.4; PRBC, packed red blood cell.

[a]$P = .012$.

[b]$P < .001$.

improvement between 61.1% and 100% was achieved for variables in the whole cohort and between 44.3% and 100% for variables in subgroup 1. The area under the receiver operating characteristic curves for the propensity scores was 0.7673 (95% CI, 0.7533–0.7813) for the whole cohort and 0.7985 (95% CI, 0.778–0.8191) for subgroup 1, respectively, demonstrating good sensitivity and specificity of the propensity scores.

Primary Outcome Parameter

We observed significant differences in the frequency of pAKF between study groups. In group RA-HES, the need for a postoperative RRT was significantly reduced compared to group RA. The corresponding data, including the number of cases, is given in Table 3. The odds ratio for patients who had received RA alone compared to those who had been given RA and HES 130/0.4 was 1.81, 95% CI, 1.08–3.04; $P = .024$. The differences in cumulative frequencies of postoperative RRT between groups are demonstrated in Supplemental Digital Content 4, Figure 1, http://links.lww.com/AA/C197.

Secondary Outcome Parameters

In-hospital mortality rates, the frequency of postoperative ICU care, and data concerning LOSH are given in Table 3 as well. Here, only 1 relevant difference could be noted: Patients belonging to group RA-HES proved to have a significantly longer LOSH when compared to group RA.

Continuous secondary outcome variables are also demonstrated in Table 3. Patients who received HES 130/0.4 had slightly (but clinically irrelevant) inferior hemodynamic conditions (MAP, heart rate), but, on the other hand, suffered from a substantially increased blood loss. Platelet and fresh frozen plasma requirements were similar between groups. Patients of group RA-HES needed significantly more crystalloids than patients of group RA itself. This result was valid when calculating the amount of crystalloids per procedure as well for crystalloids given throughout anesthesia in milliliter per kilogram bodyweight per hour.

Subgroup 1

Primary and secondary outcome variables for patients who underwent major surgery are given in Table 4. In contrast to the whole cohort, a significant difference in incidence of pAKF was not observed. The odds of developing pAKF for patients in group RA were 8% greater than for group RA-HES (odds ratio, 1.08, 95% CI, 0.49–2.41; $P = .83$). In terms of secondary outcomes, the intergroup differences are largely consistent with those of the whole cohort, including mortality rates, frequency of ICU care, LOSH, blood loss, consumption of blood products, and crystalloid requirements. The (clinically insignificant) differences in hemodynamic stability seen between groups in the whole cohort were not observed in subgroup1.

Subgroup 2

There were 1493 matched patients in whom the RIFLE criteria could be applied. Significant intergroup differences were not detected (Table 5).

Table 2. Distribution of Surgical Procedures

	All Before Matching	Crystalloid Versus HES After Matching	
		RA	RA-HES
Cardiac surgery	8.05	13.75	11.72
Endocrinologic surgery	0.94	0.74	0.65
Gynecologic surgery	12.09	5.35	4.52
Neck, nose, and ear surgery	11.20	4.70	0.83
Surgery of lymphatic tissue	1.68	1.85	1.11
Major abdominal surgery	3.65	2.86	4.89
Major neurosurgery	6.25	7.38	6.64
Major trauma surgery	16.13	12.08	17.90
Major urologic surgery	5.13	5.54	3.41
Minor abdominal surgery	9.66	9.23	19.74
Minor neurosurgery	0.72	0.65	0.00
Minor trauma surgery	3.99	3.32	0.55
Minor urologic surgery	6.03	6.83	7.66
Obstetric surgery	4.45	3.23	8.95
Orofacial surgery	0.26	0.46	0.00
Skin surgery	3.57	5.44	2.03
Thoracic and pulmonal surgery	1.45	3.14	3.23
Vascular surgery	4.73	13.47	6.18

All values are given as proportions (%). Pearson χ^2 test ($P < .001$).
Abbreviations: RA, Ringer's acetate; HES, hydroxyethyl starch 130/0.4.

Table 3. Primary and Secondary Outcome Parameters, Whole Cohort

	Crystalloid Versus HES After Matching (n = 1084/1084)		
	RA	RA-HES	*P*
Incidence of postoperative acute kidney failure requiring RRT (%)	3.78	2.12	.022
In-house mortality (%)	2.58	2.68	.492
Need for ICU therapy (%)	30.5	34.3	.062
Length of hospital stay (d)	10.0 (5/17)	12.0 (8/19)	<.001
Blood loss (mL/procedure)	406 ± 821	867 ± 1275	<.001
Fresh frozen plasma (mL/procedure)	210 ± 632	205 ± 700	.904
Platelets (mL/procedure)	63 ± 218	43 ± 066	.052
RA (mL/procedure)	1801 ± 1099	2270 ± 1115	<.001
RA throughout the duration of anesthesia (mL/kg/h)	7.8 ± 4.9	9.6 ± 5.3	.014
HES (mL/procedure)	-	500 (500/1000)	-
MAP (mm Hg)	81.5 ± 13.2	79.8 ± 10.7	.006
HR (1/min)	67 ± 15	71 ± 17	<.001

Skewed data are given as median (25th/75th percentile), normally distributed date as mean ± standardized deviation of the mean, and as proportions. Mann-Whitney *U* test for skewed data; Student *t* test for normally distributed data; Pearson χ^2 test for proportions.
Abbreviations: HES, hydroxyethyl starch 130/0.4; HR, heart rate; ICU, intensive care unit; MAP, mean arterial pressure; RA, Ringer's acetate; RRT, renal replacement therapy.

DISCUSSION

This study investigated adverse effects in patients receiving HES 130/0.4 combined with RA in comparison to those receiving exclusively RA as an intraoperative fluid replacement. A total of 9085 patients were included in the investigation. The administration of HES 130/0.4 did not induce an increased frequency of pAKF, nor did it influence mortality rates or the need for ICU care. However, perioperative blood loss in group RA-HES was as twice as high as in group RA and the treatment with HES 130/0.4 was associated with a prolonged LOSH.

Table 4. Subgroup 1: Primary and Secondary Outcome Parameters

	Crystalloid Versus HES After Matching (n = 458/458)		
	RA	RA-HES	*P*
Incidence of postoperative acute kidney failure requiring RRT (%)	2.84	2.64	.833
In-house mortality (%)	2.84	4.37	.214
Need for ICU therapy (%)	38.4	35.8	.411
Length of hospital stay (d)	12 (8/19)	14 (9/21)	.002
Blood loss (mL/procedure)	425 ± 870	849 ± 1504	<.001
Fresh frozen plasma (mL/procedure)	177 ± 599	180 ± 703	.887
Platelets (mL/procedure)	66 ± 257	35 ± 178	.032
RA (mL/procedure)	2179 ± 1239	2304 ± 1120	.031
RA throughout the duration of anesthesia (mL/kg/h)	8.8 ± 5.3	9.1 ± 5.1	.024
HES (mL/procedure)	-	729 ± 431	-
MAP (mm Hg)	82 ± 11	82 ± 10	.708
HR (1/min)	64 ± 14	66 ± 14	.069

Skewed data are given as median (25th/75th percentile), normally distributed data as mean ± standardized deviation of the mean, and as proportions. Mann-Whitney *U* test for skewed data; Student *t* test for normally distributed data; Pearson χ^2 test for proportions.

Abbreviations: HES, hydroxyethyl starch 130/0.4; HR, heart rate; ICU, intensive care unit; MAP, mean arterial pressure; RA, Ringer's acetate; RRT, renal replacement therapy.

Table 5. Subgroup 2: RIFLE Criteria in Patients With Measured Perioperative Creatinine Values

RIFLE Criteria	RA Versus RA-HES		*P*	n
No change (%)	88.4	89.6	.81	637/820
Risk (%)	7.2	6.8		
Injury (%)	3.1	2.6		
Failure (%)	1.3	0.8		

Proportions are given in %. Fisher exact test or Pearson χ^2 test for proportions, respectively. The RIFLE classification was based on serum creatinine values only. Urine output criteria were ignored.

Abbreviations: RA, Ringer's acetate; RIFLE, Risk of renal failure, Injury to the kidney, Failure of kidney function, Loss of kidney function, and End-stage renal failure; HES, hydroxyethyl starch 130/0.4.

An advantage of the statistical model used in our investigation is the possibility to generate a large database sufficiently powerful to detect intergroup differences in terms of pAKF, which is a rare event in perioperative patients (1%–7% according to ref. 24). The study population was subjected to a distinct matching process to obtain a far-reaching similarity of medically relevant conditions in the study groups. In terms of bias control, propensity score matching has been found to be more useful than other statistical methods if the treatment groups are highly imbalanced, the number of confounders is large, and/or the number of events is low.[10,25–27] This accurately describes the characteristics of the current investigations and therefore our approach should effectively mitigate the disadvantages of unmatched retrospective studies, in terms of bias and confounders.[25,26]

The potential for HES to cause kidney injury was repeatedly confirmed by numerous studies in intensive care patients.[1,2,28] However, only a minority of investigators observed an increased incidence of kidney failure in surgical patients treated with HES. Although 2 large retrospective investigations associating high-molecular weight HES with an impairment of kidney function have been recently published, to our knowledge, to date only 1 investigation indicates that HES 130/0.4 may also negatively affect the kidney in a perioperative setting.[11,29,30] On the contrary, the majority of investigators did not observe associations between low-molecular weight HES solutions and kidney injury.[5,7,31,32] The current study confirms the safety of HES 130/0.4 with regard to pAKF in a broadly diversified surgical cohort.

Unexpectedly, patients in group RA-HES developed less pAKF than patients in group RA. There are only a handful of previous investigations reporting possible positive associations between HES treatment and renal function.[33,34] Jover et al[33] observed a positive effect of HES 130/0.40 on calculated creatinine clearance. But in this investigation (n = 29), the mean clearance of the control group was exceptionally low (61.9 ± 6.6 mL/min), whereas it increased remarkably in the HES group (176.4 ± 14.3 mL/min). Thus, the relevance of our observations remains unclear especially because we found neither significant intergroup differences in subgroup 1 (Table 4) nor observed significant perioperative changes of the RIFLE classes (subgroup 2, Table 5). With a change rate of the RIFLE classes between 0.8% and 6.8% and between 1.3% and 7.2% ($P > .05$), respectively, the current data are consistent with other investigations.[35]

To date, studies reporting higher mortality rates when administering HES preparations exclusively derive from the field of ICU care.[1,28] Thus, our findings that in-hospital mortality rates and the frequency of postoperative ICU care are unrelated to HES administration is consistent with the literature. In contrast, study results concerning a possible influence of modern HES solutions on intraoperative blood loss are still conflicting. In 1 meta-analysis and 2 retrospective trials, an increased blood loss could only be associated with high-molecular weight HES preparations, but not with HES 130/0.4.[6,29,30] However, these results are in contradiction to 2 randomized controlled trials recently published by Kancir et al.[31,32] In this study, HES therapy was associated with a blood loss more than twice as high as with RA alone. When evaluating this result, several factors must be considered. First, blood loss usually depends on the type of surgery, which, despite the matching process, was not perfectly balanced between groups (Table 2). However, the number of patients in cardiac and vascular surgery, usually most predisposed to severe blood loss, was higher in group RA.[36] Second, secondary outcomes in subgroup 1 confirmed the increased blood loss in group RA-HES. Summarizing, we cannot exclude that intergroup differences in blood loss were truly associated with HES 130/0.4 administration and not artifacts generated by a study-related bias or confounders. Additionally, our results are in accordance with a meta-analysis published by Rasmussen.[37]

Patients in group RA-HES received significantly more crystalloids than patients in group RA (Table 3). This can be explained by the increased blood loss experienced by patients in group RA-HES, which was not fully compensated by the administration of HES and PRBC. This presumption can be substantiated by some basic calculations that are given in Supplemental Digital Content 2, Table A2/4 in Appendix 2, http://links.lww.com/AA/C195. It becomes evident that the amount of crystalloid given closely matches the requirements for isovolemia maintenance in both groups.[38,39] The adjusted fluid balance for

crystalloids was +101 mL for patients of group RA and +30 mL for patients of group RA-HES, respectively. Treatment with HES 130/0.4 was also associated with a prolonged LOSH. The reason for this is unclear. However, one can speculate that the increased blood loss in group RA-HES may have contributed to this result.

Limitations

In this investigation, we configured the matching procedure as effective as possible. However, there are several indicators suggesting that the matching process was good, but not perfect. First, the type of surgery, PRBC, and noradrenaline requirements could not be completely balanced between groups. Second, LOSH was significantly shorter in group RA. We could not discriminate whether participants of group RA were less affected by the surgical process or whether this effect was caused by greater blood losses in group RA-HES. Nevertheless, the matching process was highly effective, leading to a variable balance improvement up to 100% (Supplemental Digital Content 3, Appendix 3, http://links.lww.com/AA/C196).[35,40]

Defining pAKF as the need for first time RRT may also be questionable because the decision when to start RRT differs among health care providers. This implicates the danger of a personal bias. However, this affected both groups equally and should not have influenced intergroup comparisons. Though well defined by institutional SOPs and controlled by senior anesthetists, the amount of fluid administered could not be controlled by the study protocol due to the retrospective nature of this investigation. This may be regarded as a relevant confounder. However, fluid administration was moderate in both study groups and largely similar to other investigations.[32] Furthermore, given this affected both groups equally, it should have had little influence on the results of this investigation. Finally, it must be stated that we exclusively evaluated HES 130/0.4. Therefore, the results of this investigation are not valid for other HES preparations currently available.

CONCLUSIONS

In this propensity score matched cohort study, we did not find an association between HES 130/0.4 therapy and pAKF, when compared to crystalloids alone. HES 130/0.4 did not negatively influence mortality and the need for ICU therapy. However, the use of this colloid was associated with an increased blood loss.

DISCLOSURES

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Contribution: This author helped design the study, conduct the study, analyze the data, and write the manuscript.
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Contribution: This author helped design the study, analyze the data, and review the manuscript.
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