# No Differences in Renal Function between Balanced 6% Hydroxyethyl Starch (130/0.4) and 5% Albumin for Volume Replacement Therapy in Patients Undergoing Cystectomy

## *A Randomized Controlled Trial*

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## ABSTRACT

**Background:** The use of artificial colloids has declined in critical care, whereas they are still used in perioperative medicine. Little is known about the nephrotoxic potential in noncritically ill patients during routine surgery. The objective of this trial was to evaluate the influences of albumin 5% and balanced hydroxyethyl starch 6% (130/0.4) on renal function and kidney injury.

**Methods:** One hundred urologic patients undergoing elective cystectomy were randomly assigned for this prospective, single-blinded, controlled study with two parallel groups to receive either albumin 5% or balanced hydroxyethyl starch 6% (130/0.4) as the only perioperative colloid. The primary endpoint was the ratio of serum cystatin C between the last visit at day 90 and the first preoperative visit. Secondary endpoints were estimated glomerular filtration rate and serum neutrophil gelatinase-associated lipocalin until the third postoperative day and risk, injury, failure, loss, and end-stage renal disease criteria at postoperative days 3 and 90.

**Results:** The median cystatin C ratio was 1.11 (interquartile range, 1.01 to 1.23) in the albumin and 1.08 (interquartile range, 1.00 to 1.20) in the hydroxyethyl starch group (median difference = 0.03; 95% CI, –0.09 to 0.08; $P = 0.165$). Also, there were no significant differences concerning serum cystatin C concentrations; estimated glomerular filtration rate; risk, injury, failure, loss, and end-stage renal disease criteria; and neutrophil gelatinase-associated lipocalin. Infusion requirements, transfusion rates, and perioperative hemodynamics were similar in both groups.

**Conclusions:** With respect to renal function and kidney injury, this study indicates that albumin 5% and balanced hydroxyethyl starch 6% have comparable safety profiles in noncritically ill patients undergoing major surgery. **(Anesthesiology 2018; 128:67-78)**

THE use of infusion solutions containing artificial colloids, especially hydroxyethyl starch (HES), has almost declined to zero in critical care patients worldwide due to their potential nephrotoxic side effects and increased mortality, as shown in some studies.[1,2] The conclusions drawn from these trials were highly controversial. Criticisms included the HES preparations used, as well as the initial volume therapy before random assignment of these patients.[3,4] Some authors argued that HES was not applied according to an adequate dosage and indication, and therefore is still a safe volume expander, whereas other authors concluded that HES should be banned generally.[5,6] Some recent randomized controlled trials found no evidence for nephrotoxicity of artificial colloids when used in a perioperative setting in noncritically ill patients.[7,8] Regardless of potential differences between critically ill and otherwise healthy intraoperative patients, the use of artificial colloids also declined in the operative setting during the past years.

Under the conditions of a severe acute blood loss, substitution by a threefold volume of lactated Ringer's solution is not sufficient to maintain intravascular normovolemia.[9] Instead, highly positive fluid balances are regularly needed. To overcome excessively positive fluid balances, colloids

### What We Already Know about This Topic

- Hydroxyethyl starch causes renal injury when given in high doses over prolonged periods to critically ill patients.
- Whether starches cause more renal toxicity than albumin in perioperative patients remains unclear.

### What This Article Tells Us That Is New

- One hundred surgical patients were randomly assigned to hydroxyethyl starch (130 kilodaltons) or albumin.
- The primary endpoint was the change in cystatin C on postoperative day 90. Secondary endpoints were estimated glomerular filtration rate and serum neutrophil gelatinase-associated lipocalin until postoperative day 3 and risk, injury, failure, loss, and end-stage renal disease criteria up to postoperative day 90.
- There were no significant differences in any outcome, suggesting that starches do not cause more renal injury than albumin.

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persist as an important tool for maintaining hemodynamic stability in otherwise unstable patients.[10,11] Nevertheless, the current recommendations for substitution rely on a crystalloid–based stage concept for volume therapy.[12] This includes the recommendation that only blood losses exceeding 20% of the patient's blood volume be treated with colloid solutions, addressing the fact that HES may only be used if blood loss cannot be treated by crystalloids alone. From a pathophysiological point of view, however, replacement of blood and protein losses with colloids in a ratio of 1:1 would be more useful and probably beneficial concerning patient outcomes.[13] A possible alternative to artificial colloids in this setting could be albumin. The safety of albumin in intensive care medicine was investigated and confirmed in a large trial in 2004.[14] Until now, however, there were insufficient data published investigating the superiority of albumin over HES on renal safety in perioperative patients.

To measure potential nephrotoxic side effects of colloids, routine laboratory parameters such as creatinine, blood urea nitrogen, or the estimated glomerular filtration rate were used in most of the previous trials.[2,15] Although serum creatinine and the glomerular filtration rate (GFR) calculated by the Cockroft–Gault formula are of limited value in patients with only minor changes in renal function, cystatin C is a highly sensitive parameter for detecting early kidney injury independent from race, sex, or comorbidities.[16–18]

We therefore designed a prospective, randomized, single-blinded trial in a perioperative setting with noncritically ill patients to compare the balanced HES 6% (130/0.4) with 5% albumin. The primary endpoint was the ratio of serum cystatin C within an observation period of 90 days.

## Materials and Methods

The study was planned as a single-center, single-blinded, prospective randomized trial with two parallel groups (randomization ratio 1:1) to compare albumin 5% (study drug) and balanced 6% HES 130/0.4 (Volulyte, Fresenius Kabi, Germany; comparator). Ethical approvals were obtained from the ethics committee of the Ludwig-Maximilians-University of Munich (Munich, Germany; reference No. 311-11) and the responsible drug administration authority (Paul-Ehrlich-Institute of the German Federal Ministry of Health, Langen, Germany). The study was registered at the European Medical Association (Brussels, Belgium; EudraCT No. 2010-018343-34; registration: July 26, 2011). The trial was conducted from May 2012 to May 2015 at the Hospital of the University of Munich (Munich, Germany). The authors prepared this study report in accordance with the Consolidated Standards of Reporting Trials guidelines.[19] The trial was conducted in accordance with the original protocol published in 2015.[20]

### Study Participants

After screening and obtaining written informed consent, adult patients from 18 to 85 yr with American Society of Anesthesiologists (ASA) physical status classifications I to IV scheduled for surgical cystectomy were eligible for this prospective randomized trial. All of the patients experienced cancer of the urinary tract and were planned either to receive an ileum conduit or a neobladder by the institutional urologists. Eligible patients were provided an information form describing the trial in detail. Exclusion criteria included unfavorable prognosis (*e.g.*, palliative surgical care in cases of obstruction of the efferent urinary tract), evidence of metastatic disease, coagulopathy or platelet dysfunction, preoperative creatinine clearance less than 30 ml/min, preoperative chemotherapy with a nephrotoxic drug (*e.g.*, cisplatin), application of colloidal infusion solutions within the past 24 h before surgery, history of hypersensitivity to one of the investigational drugs, abuse of drugs or alcohol, simultaneous participation in another clinical trial, current pregnancy or nursing women, and women of childbearing potential without reliable methods of contraception for the entire study duration.

### Preoperative Care

After inclusion into the clinical trial and informed consent, all of the patients were interviewed using a standardized questionnaire to detect coagulopathies. In addition to routine preoperative laboratory parameters (creatinine, C-reactive protein, hemoglobin, platelet and leukocyte counts, prothrombin time, and partial thromboplastin time), the serum cystatin C concentrations were measured. The use of colloids before the surgical intervention was prohibited.

### Intraoperative and Postoperative Care

All of the patients received general anesthesia, usually combined with a thoracic epidural anesthesia. In case of a contraindication to neuraxial block, postoperative patient-controlled analgesia was started in the recovery room. The anesthetic technique was standardized for all of the patients. For epidural analgesia, ropivacaine 0.2% in combination with epidural sufentanil was used. General anesthesia was induced with propofol (2.0 mg/kg), sufentanil (0.4 μg/kg), and rocuronium (0.6 mg/kg) and maintained with propofol (5 $mg \cdot kg^{-1} \cdot h^{-1}$) or sevoflurane (0.8 to 1.0 minimum alveolar concentration; fresh gas flow rate 1 to 2 l/min) in combination with remifentanil (0.1 $\mu g \cdot kg^{-1} \cdot min^{-1}$ each). Standard monitoring (electrocardiogram, pulsoxymetry, temperature, and noninvasive blood pressure) was applied in all patients. This was combined with invasive blood pressure measurement *via* a radial artery. In addition, all of the patients received a central venous catheter for application of vasopressors or catecholamines if needed. Advanced hemodynamic monitoring was performed using the Vigileo Monitor with FloTrack-Sensor (Edwards Lifesciences Corporation, USA) until transfer to the ward. During anesthesia, all of the clinical parameters and medications were recorded by online documentation software (NarkoData, IMESO GmbH, Germany).

The perioperative application of infusion solutions, vasoactive drugs, and blood transfusions was subject to a goal directed protocol (see table A, Supplemental Digital Content, http://links.lww.com/ALN/B548), which is a protocol including hemodynamic target parameters and recommendations for fluid therapy, vasopressors, catecholamines, and erythrocyte transfusion). This protocol was part of the patient file and was available to the attending physicians at any time. Deviations from the protocol were allowed. Cell-free fluid losses (urine output and perspiratio insensibilis up to 500 ml) were replaced with a balanced acetated Ringer's solution in a 1:1 ratio. Blood loss was replaced by either albumin 5% or HES 6% (130/0.4) in a 1:1 ratio until a specific transfusion trigger was reached or to a maximum volume of 30 ml · $kg^{-1}$ · $day^{-1}$. The additional use of colloidal infusion solutions between postoperative days 4 and 90 was prohibited by protocol.

After surgery, all of the patients were transferred to the recovery room and from there, after being evaluated by the attending anesthetist, assigned either to the intensive care unit for closely surveyed recovery or to the regular ward, where they stayed until discharge from the hospital. Postoperative pain management was achieved by patient-controlled epidural anesthesia. In case of contraindications for or failure of epidural block, patient-controlled analgesia with piritramide was retained for at least 3 days. All of the patients were visited by one of the investigators 2 to 4 h after surgery and on postoperative days 1 and 3.

### Laboratory Parameters and GFR Estimation

Laboratory parameters were obtained before, during, and after the surgical intervention. Cystatin C concentration, as a parameter for GFR,[21] was measured preoperatively; at the end of the surgical procedure; and on postoperative days 1, 3, and 90 using a turbidimetric immunoassay (range, 0.1 to 10.0 mg/l; reference range, 0.61 to 1.11 mg/l; variation coefficient, 1.83% at 0.83 mg/l and 0.96% at 4.06 mg/l; Biomed Diagnostics GmbH, Germany) with a stand-alone analyzer (AU 5800; Beckman Coulter GmbH, Germany). Measurements were done once, if values were within range of the assay. A total of 9 ml whole blood was withdrawn for each determination, immediately centrifuged (3,500 U/min for 10 min) and stored at –70°C. Serum neutrophil gelatinase-associated lipocalin, a marker of tubular injury, was measured after anesthesia induction, at the end of the surgical procedure, 2 to 4 h postoperatively, and on postoperative days 1 and 3 using the NGAL ELISA kit 036 (Bioporto Diagnostics, Denmark).[22] All of the other parameters were measured by routine laboratory tests. The laboratory staff was blinded to the both treatment groups. GFR was estimated using serum cystatin C: estimated GFR (ml · $kg^{-1}$ · 1.73 $m^{-2}$) = 130 × cystatin $C^{-1,069}$ × $age^{-0.117}$ – 7.[16]

### Follow-up

All of the patients received a telephone call and were interviewed using a standardized questionnaire on postoperative day 90 after surgery. In this interview they were specifically asked for additional hospital stays after discharge from the primary hospital, potential adverse events, therapy with colloids after discharge, and incidence of pruritus.

### Outcome Measures

The aim of the study was to detect a possible superiority of albumin 5% over HES 6% (130/0.4) by measuring the serum cystatin C ratio between postoperative day 90 and preoperative values. These differences were regarded as primary outcome parameters. Secondary outcome parameters were as follows: (1) estimated GFR; (2) serum neutrophil gelatinase-associated lipocalin as a parameter for kidney injury; and (3) risk, injury, failure, loss, and end-stage renal disease (RIFLE) criteria at postoperative days 3 and 90. Additional parameters were change of serum cystatin C levels over time, crystalloid and colloid requirements, transfusion rates, and need for vasopressors and catecholamines up to postoperative day 3.

### Statistics

**Sample Size Estimation.** The study was designed with an intention-to-treat approach to detect a difference in serum cystatin C translating into a 20% decrease of the GFR for the HES group compared with the human albumin group, which was considered a clinically relevant change (two-sided Mann–Whitney U test, α level of 0.05, power of 0.8). We calculated a sample size of 47 per group to be required. Based on previous experience, we estimated the dropout rate to be approximately 10%. To compensate for these dropouts and slight imbalances in the allocation rates to the treatment groups, we planned to enroll 105 patients in total (50 to 55 per treatment group).

### Randomization

Open-label randomization was performed in a ratio of 1:1 using randomized balanced blocks with random block lengths using a proprietary Web-based randomization tool (Randoulette). The procedure considered stratification by type of surgical procedure (ileum conduit or neobladder). The allocation sequence was generated by a study statistician. Evaluation of the eligibility, obtaining informed consent, and enrollment of participants were accomplished by a research assistant who was registered as a study investigator.

### Statistical Methods

All of the analyses were based on the intention-to-treat principle. The variables were described using appropriate measures of location and dispersion. Before statistical analysis, the data analyst was blinded for the two groups. The primary efficacy analysis of cystatin C changes between baseline and day 90 relied on a confirmatory two-sided Mann–Whitney U test on an α level of 0.05. In cases of missing cystatin C values at day 90 (11 patients in the albumin group and 4 patients in the HES group), we imputed a value greater than the observed cystatin C ratios, ensuring that these patients entered the analysis with

the highest, that is, most pessimistic ranks for the U test. All of the other tests should be regarded as exploratory in nature. The 95% confidence limits for the median difference were based on a quantile regression analysis using the SAS QUANTREG procedure (SAS Institute Inc., USA). Secondary outcomes were analyzed using Mann–Whitney U tests in case of metrical analysis variables and Fisher two-sided exact test for dichotomous variables. Due to the exploratory nature of these analyses, we did not adjust the α level for multiple testing, comparing the resulting *P* values with the local α level of 0.05. Serum cystatin C and neutrophil gelatinase-associated lipocalin changes over time were analyzed by means of random intercept models using the SAS GLIMMIX procedure (SAS Institute Inc.). *Post hoc* tests were adjusted using the Bonferroni method.[23] Safety parameters were analyzed descriptively. Subgroups and additional variables that were not specified as primary or secondary endpoints were considered by *post hoc* analysis. All of the analyses were performed using SAS version 9.3 for Linux (SAS Institute Inc.) and SPSS statistics version 23 for Windows (IBM Corporation, USA).

### Data Safety Monitoring Board and Interim Analysis

In June 2013 the European Medicines Agency Pharmacovigilance Risk Assessment Committee (London, United Kingdom) concluded, after a review of available evidence, that the benefits of infusion solutions containing HES would no longer outweigh their risks and therefore recommended completely stopping the administration of HES and suspending the marketing authorization.[24] Of course, these recommendations were also of concern for the ongoing study. Recruitment of new patients had to be paused from June 2013. An independent data safety monitoring board was established to assess the progress of the study and the safety data. Between June 2013 and March 2014, the Pharmacovigilance Risk Assessment Committee recommendations were in part revised by the European Medicines Agency and the Coordination Group for Mutual Recognition and Decentralized Procedures–Human (Federal Institute for Drugs and Medical Device, Bonn, Germany). The use of HESs remained prohibited in patients with sepsis, burn injuries, or those who were critically ill but was now reauthorized in patients with hypovolemia caused by acute (sudden) blood loss.[25,26] After consideration of these new recommendations, the study was continued in February 2014. A previously planned interim inspection of the date was to be performed in midcourse to check the assumptions of our initial sample size calculation and to allow for a reestimation based on the principle of conditional rejection probabilities if necessary.[27,28] The conditional rejection probabilities principle allows sample size reestimation without formal testing and thus without α spending and without the necessity of correcting the α level. No statistical adjustments were done after the interim inspection.

## Results

A total of 131 patients were screened for participation, of whom 31 had to be excluded (14 patients declined, 2 withdrew consent, 14 met exclusion criteria, and 1 was excluded for other reasons). A total of 100 patients were randomly assigned (albumin: n = 53, HES: n = 47). The participant flow diagram is shown in figure 1. All of the patients received a radical cystectomy with either construction of a neobladder (n = 50) or an ileum conduit (n = 50). The demographic data of participants were similar in both groups without any significant differences (table 1). None of the patients received a colloid infusion before surgical intervention or after the first postoperative day. The mean volume of crystalloid infusion given until the third postoperative day was comparable in both groups, whereas in the direct perioperative period (until postoperative day 1), significantly more crystalloids were administered in the albumin group ($P$ = 0.042). The average volume of perioperative colloid infusion until postoperative day 1 was higher in the HES group than in the albumin group ($P$ = 0.026). Unfortunately, one patient in the HES group accidentally received 100 ml albumin 20% in the recovery room, and two patients of the HES group received 100 ml, respectively 200 ml of albumin 20% at postoperative day 1. Also, two patients in the albumin group accidentally received 500 ml HES solution at postoperative day 1. The intraoperative transfusion rates for erythrocytes and fresh-frozen plasma were not significantly different. All of the infusion requirements and transfusion rates are given in table 2. Durations of surgery and anesthesia, hemoglobin values, hemodynamic variables, and vasoactive medications were also comparable between both groups (table 3).

Serum cystatin C concentrations on the day before surgery; immediately after the surgical procedure; and on postoperative days 1, 3, and 90 showed no significant differences between both groups. Accordingly, the GFR values, estimated by using the individual serum cystatin C values, displayed no significant differences between groups at the corresponding time points (fig. 2). With respect to the primary study endpoint (cystatin C ratio between postoperative day 90 and preoperative values), no statistically significant difference was observed between groups (albumin group = 1.11; interquartile range, 1.01 to 1.23; HES group = 1.08; interquartile range, 1.00 to 1.20; median difference = 0.03; 95% CI, –0.09 to 0.08; $P$ = 0.165; table 4).

Concerning intragroup changes, we found significant postoperative changes of median serum cystatin C compared with their preoperative controls. Cystatin C decreased in both groups until postoperative day 3, whereas an increase was found between preoperative controls and postoperative day 90 in the albumin group. After 3 months, cystatin C concentrations were measured in 42 patients of the albumin group and in 43 patients of the HES group. Of these patients, more than 80% in both groups had an estimated GFR decline of less than 25% (no acute kidney injury according to the RIFLE criteria defined by Bellomo *et al.*[29]). The incidences

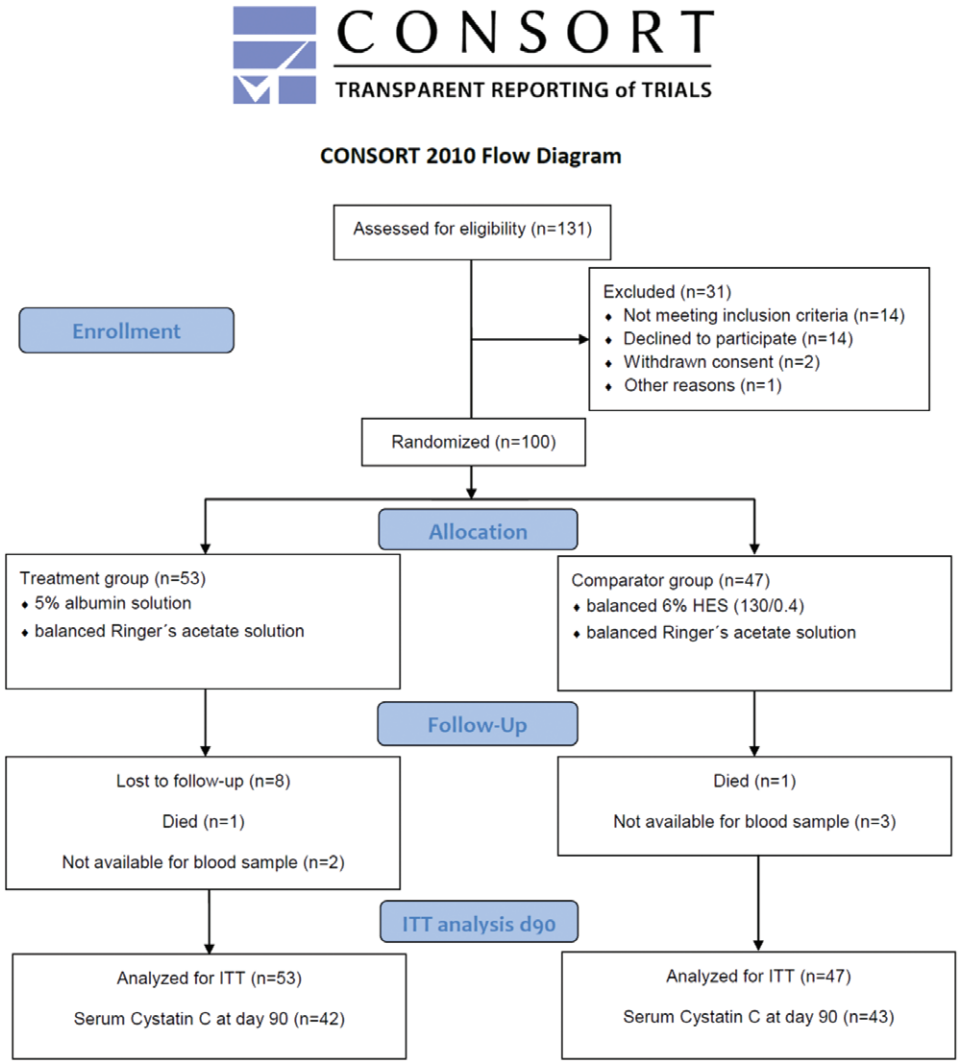


**Fig. 1.** Participant flow diagram.

**Table 1.** Demographic Data

| | Albumin (N = 53) | HES (N = 47) | *P* Value |
|---|---|---|---|
| Ileum conduit/neobladder, n | 26/27 | 24/23 | 1.000 |
| Sex distribution, n (%) | | | 0.201 |
| Women | 13 (24.5) | 6 (12.8) | |
| Men | 40 (75.5) | 41 (87.2) | |
| Age, yr | 70 (61–75) | 70 (63–75) | 0.435 |
| Height, m | 1.76 (1.70–1.81) | 1.74 (1.69–1.80) | 0.509 |
| Body weight, kg | 82 (70–92) | 75 (69–90) | 0.388 |
| Body mass index, kg/m$^2$ | 26.7 (24–30) | 25.6 (23.6–28.4) | 0.464 |
| ASA classification, n (%) | | | 0.054 |
| I | 4 (7.5) | 2 (4.3) | |
| II | 14 (26.4) | 24 (51.1) | |
| III | 34 (64.2) | 29 (42.6) | |
| IV | 1 (1.9) | 1 (2.1) | |

Metric values are given as median (interquartile range). Mann–Whitney U test was used for metrical variables and Fisher exact test (two-sided) for dichotomous variables.

ASA = American Society of Anesthesiologists; HES = hydroxyethyl starch.

**Table 2.** Infusion Requirements, Blood Loss, and Transfusion Rates

| | Albumin (N = 53) | HES (N = 47) | *P* Value |
|---|---|---|---|
| Crystalloid requirements, ml | | | |
| Total crystalloid requirements during SP | 10,894 ± 2,533 | 11,116 ± 2,839 | 0.722 |
| Until transfer to ICU, PACU, or regular ward | 3,328 ± 1,120 | 2,955 ± 1,043 | 0.042 |
| From transfer to POD 1 | 2,689 ± 1,134 | 2,912 ± 1,429 | 0.399 |
| From POD 1 to 3 | 4,877 ± 1,706 | 5,250 ± 1,963 | 0.429 |
| Colloid requirements, ml* | | | |
| Total colloid requirements during SP | 1,705 ± 879 | 2,000 ± 969 | 0.082 |
| Until transfer to ICU, PACU, or regular ward | 1,577 ± 684 | 1,940 ± 828 | 0.026 |
| From transfer to POD 1 | 127 ± 316 | 60 ± 300 | 0.185 |
| From POD 1 to 3 | 0 ± 0 | 0 ± 0 | 1.000 |
| Blood loss and drainage amount, ml | | | |
| Estimated intraoperative blood loss | 1,126 ± 549 | 1,127 ± 618 | 0.771 |
| Drainage volume from transfer to POD 1 | 288 ± 256 | 222 ± 169 | 0.261 |
| Drainage volume from POD 1 to 3 | 383 ± 432 | 350 ± 447 | 0.206 |
| Transfusion rates, n (%) | | | |
| Total transfusion rates during SP | | | |
| Erythrocyte | 22 (41.5) | 17 (36.2) | 0.682 |
| Fresh-frozen plasma | 8 (15.1) | 3 (6.4) | 0.210 |
| Platelet | 1 (1.9) | 0 (0) | 1.000 |
| Intraoperative | | | |
| Erythrocyte | 17 (32.1) | 11 (23.4) | 0.378 |
| Fresh-frozen plasma | 7 (13.2) | 3 (6.4) | 0.328 |
| Platelet | 0 (0) | 0 (0) | |
| Until POD 1 | | | |
| Erythrocyte | 9 (17.0) | 8 (17.0) | 1.000 |
| Fresh-frozen plasma | 2 (3.8) | 0 (0) | 0.497 |
| Platelet | 1 (1.9) | 0 (0) | 1.000 |
| Until POD 3 | | | |
| Erythrocyte | 5 (9.4) | 4 (8.5) | 1.000 |
| Fresh-frozen plasma | 0 (0) | 0 (0) | |
| Platelet | 0 (0) | 0 (0) | |

Metric values are given as mean ± SD. Mann–Whitney U test was used for metrical variables and Fisher exact test (two-sided) for dichotomous variables.
*Data are shown without erythrocyte, fresh-frozen plasma, and platelet transfusion.
HES = hydroxyethyl starch; ICU = intensive care unit; PACU = postanesthesia care unit; POD = postoperative day; SP = study period.

of stage risk (GFR decrease greater than 25%) and stage injury (GFR decrease greater than 50%) at postoperative days 3 and 90 were comparable in both groups. Only one patient of the albumin group required temporary postoperative renal replacement therapy by hemofiltration. For median serum neutrophil gelatinase-associated lipocalin, we found no significant intragroup changes in both groups compared with preoperative values, as well as no differences between the groups. All of the parameters concerning renal function, kidney injury, and RIFLE criteria are given in table 4.

Transfer rates to intensive care unit were comparable in both groups (albumin group = 47.2%; HES group = 48.9%; $P = 0.841$). In a *post hoc* analysis comparing intensive care and nonintensive care patients in both groups, we found no differences regarding serum cystatin C, serum neutrophil gelatinase-associated lipocalin, and estimated GFR in the postoperative period. Significant differences between intensive care and nonintensive care patients were obtained, that is, regarding total colloid requirements (albumin group: 2,080 ± 971 *vs.* 1,370 ± 635 ml; $P = 0.004$; HES group: 2,308 ± 1,087 *vs.* 1,678 ± 719 ml; $P = 0.038$), erythrocyte transfusion rate during study period (albumin group: 60% *vs.* 25%; $P = 0.013$; HES group: 62.5% *vs.* 8.7%; $P < 0.0001$), and need of norepinephrine at postoperative day 1 (albumin group: 56% *vs.* 0%; $P < 0.0001$; HES group: 54.2% *vs.* 0%; $P < 0.0001$). In the HES group, total crystalloid requirements during postoperative day 3 were significantly higher in intensive care patients compared with nonintensive care patients (12,052 ± 2,884 *vs.* 10,139 ± 2,490 ml; $P = 0.019$; table 5).

The duration of hospital stay was comparable among both groups (HES group: 20 ± 9 days; albumin group: 22 ± 16 days; $P = 0.165$). The incidence of pruritus, evaluated by a standardized questionnaire at day 90, was 2.1% (n = 1) in the HES group and 15.1% (n = 8) in the albumin group ($P = 0.014$).

## Discussion

This prospective, randomized, single-blinded trial with 100 elective surgical patients analyzed parameters of renal function and kidney injury. When administered in a perioperative setting, no significant differences between albumin 5% and

**Table 3.** Duration of Procedures, Hemodynamics, and Vasoactive Medication

| | Albumin (N = 53) | *P* Value | HES (N = 47) | *P* Value | *P* Value |
|---|---|---|---|---|---|
| Duration of surgery, min | 225 (183/278) | | 225 (170/274) | | 0.421 |
| Duration of anesthesia, min | 315 (278/385.5) | | 312 (263/367) | | 0.485 |
| Hemoglobin, g/dl | | | | | |
| Before surgery | 12.7 (11.5/14.1) | | 12.5 (11.1/13.7) | | 0.641 |
| After surgery | 9.7 (8.8/11) | | 9.8 (8.4/11) | | 0.636 |
| Lowest intraoperative value | 9.3 (8.2/10.6) | | 9.2 (8.1/10.1) | | 0.548 |
| Cardiac index, $l \cdot min^{-1} \cdot m^{-2}$ | | | | | |
| After induction of anesthesia | 2.30 (2.10/2.60) | | 2.32 (2.18/2.52) | | 1.000* |
| After 1 h | 2.50 (2.26/2.89) | 0.431*† | 2.52 (2.22/2.70) | 0.066*† | 1.000* |
| After 2 h | 2.60 (2.35/3.00) | 0.001*† | 2.60 (2.40/3.05) | < 0.001*† | 1.000* |
| At the end of surgery | 2.90 (2.59/3.58) | < 0.0001*† | 2.80 (2.50/3.55) | < 0.0001*† | 1.000* |
| Stroke volume variation, % | | | | | |
| After induction of anesthesia | 8 (6/10) | | 9 (6/12) | | 1.000* |
| After 1 h | 10 (7/12) | 1.000*† | 10 (7/13) | 1.000*† | 1.000* |
| After 2 h | 10 (7/13) | 0.257*† | 9 (6/11) | 1.000*† | 1.000* |
| At the end of surgery | 9 (6/12) | 1.000*† | 9 (7/11) | 1.000*† | 1.000* |
| Percentage of time of low MAP during anesthesia | 10 (4.5/19) | | 7 (2/15) | | 0.363 |
| Lowest MAP during anesthesia, mmHg | 54 (45.5/58) | | 53 (49/58) | | 0.722 |
| Maximum norepinephrine, $\mu g \cdot kg^{-1} \cdot min^{-1}$ | | | | | |
| Intraoperative | 0.14 (0.09/0.21) | | 0.14 (0.1/0.2) | | 0.809 |
| POD 1 | 0 (0/0.03) | | 0 (0/0.04) | | 0.777 |
| POD 3 | 0 (0/0) | | 0 (0/0) | | 0.573 |
| Need for norepinephrine, n (%) | | | | | |
| Intraoperative | 53 (100) | | 47 (100) | | – |
| POD 1 | 14 (26.4) | | 13 (27.7) | | 1.000 |
| POD 3 | 4 (7.5) | | 5 (11.6) | | 0.731 |
| Need for vasopressin, n (%) | | | | | |
| Intraoperative | 0 (0) | | 2 (4.2) | | 0.218 |
| POD 1 | 1 (1.9) | | 1 (2.1) | | 1.000 |
| POD 3 | 0 (0) | | 1 (2.1) | | 0.470 |
| Need for epinephrine, n (%) | | | | | |
| Intraoperative | 2 (3.8) | | 3 (6.4) | | 0.664 |
| POD 1 | 1 (1.9) | | 2 (4.2) | | 0.599 |
| POD 3 | 0 (0) | | 1 (2.1) | | 0.470 |
| Need for dobutamine, n (%) | | | | | |
| Intraoperative | 4 (7.6) | | 2 (4.2) | | 0.681 |
| POD 1 | 1 (1.9) | | 0 (0) | | 1.000 |
| POD 3 | 0 (0) | | 0 (0) | | – |

Metric values are given as median (interquartile range). Low MAP was defined as less than 70 mmHg for American Society of Anesthesiologists (ASA) III and IV patients and less than 60 mmHg for ASA I and II patients. Mann–Whitney U test was used for metrical variables and Fisher exact test (two-sided) for dichotomous variables.

*Data show adjusted *P* values in repeated measurements using Bonferroni correction. †Data show comparison with baseline values.

MAP = mean arterial pressure; POD = postoperative day.

balanced 6% HES solution (130/0.4) were observed regarding cystatin C and estimated GFR in the immediate postoperative period until postoperative day 90. Also, no significant differences could be detected for serum neutrophil gelatinase-associated lipocalin up to the third postoperative day.

These results are in good agreement with an investigation by Kancir *et al.*,[7] comparing nonbalanced 6% HES solution (130/0.4) with isotonic saline in 38 patients during hip arthroplasty. No harmful renal effects were observed regarding urinary neutrophil gelatinase-associated lipocalin and serum creatinine up to postoperative day 12. Bartz *et al.*[30] examined clinical and renal outcomes of 4,888 postoperative patients after converting from high molecular weight (450/0.7) to low molecular weight hetastarch (130/0.4). This change resulted in decreased albumin requirements without differences in clinical outcomes and mortality. The effects of HES 6% (130/0.4) compared with 5% albumin were also assessed in a randomized trial in pediatric cardiac surgery by van der Linden *et al.*[31] No differences were detected concerning blood loss, transfusion requirements, and renal function. The authors concluded that HES 6% (130/0.4) was equivalent to albumin 5% with regard to volume replacement, thereby extending the data from other trials in adult patients.[32]

In 2011 a meta-analysis by Groeneveld *et al.*[33] of 42 randomized controlled trials including 10,382 patients showed

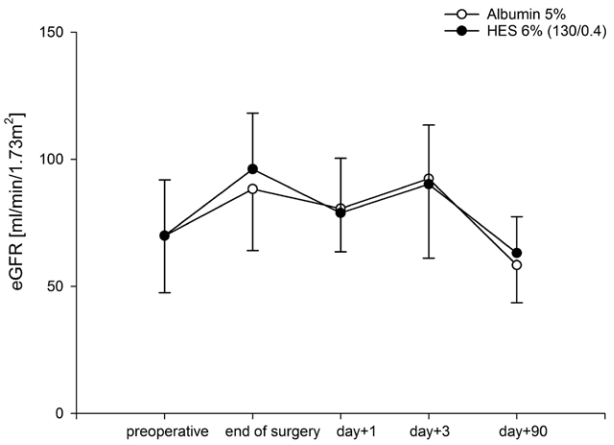


**Fig. 2.** Estimated glomerular filtration rate (eGFR); median (interquartile range). HES = hydroxyethyl starch.

a favorable safety profile for albumin compared with HES, whereas the available evidence did not support differences between the individual HES solutions. However, it is still a matter of debate whether older high-molecular-weight HESs should be included in meta-analyses or whether comparisons should be limited to the recent low-molecular-weight forms.[34] A meta-analysis by Martin *et al.*[35] included 17 clinical trials with 1,230 patients and different kinds of surgeries. All of the trials compared 6% HES (130/0.4) with other colloids or crystalloids. There was no evidence that the incidence of renal dysfunction was different. In their review analyzing 59 studies with 4,529 patients, van der Linden *et al.*[34] evaluated the safety of HES during surgery in noncritically ill patients. Again, there was no evidence for adverse renal effects, nor was tetrastarch followed by increased blood loss, transfusion requirement, or mortality. However, most included trials used unsuitable comparators like older starch solutions or crystalloids. Only a few controlled trials compared HES with albumin. Cystatin C was not assessed in these studies, and additional parameters of renal function were evaluated in a limited number of patients only. In addition, some studies were criticized for their too-short observation periods.[36] These shortcomings could limit the clinical value of the respective meta-analyses with respect to long-term renal outcome.[36–38]

Comparing hetastarch and tetrastarch solutions, Gandhi *et al.*[39] demonstrated a comparable plasma volume effect in a randomized controlled trial in patients undergoing major orthopedic surgery. As primary safety endpoints, the authors measured the effects on coagulation by nadirs of factor VIII activity and von Willebrand factor activity and were able to show a lower effect on coagulation of HES 6% (130/0.4) compared with HES 6% (670/0.75). In addition, the totals for transfused erythrocytes for those patients requiring transfusion were significant higher.[39]

A meta-analysis by Jacob *et al.*[40] compared the impact of different HES solutions in cardiac surgery. No differences were found when low-molecular-weight tetrastarch (130/0.4) was compared with albumin, gelatine, or crystalloid solutions. With respect to safety, the authors were unable to identify any disadvantages of tetrastarch. However, this meta-analysis was criticized due to a potential bias concerning the included studies, too.[41]

In the current trial, 38.3% of the patients in the HES group and 34.6% in the albumin group had a preoperative estimated GFR of less than 60 ml · min$^{-1}$ · 1.73 m$^{-2}$ and thus met the criteria for chronic kidney disease classified by the Kidney Disease Quality Outcome Initiative.[42,43] Until postoperative day 90, these rates increased to 42.9% (HES group) and 53.5% (albumin group). This increase was statistically significant within the albumin group, whereas no statistical significance was reached between groups. In addition, focusing on patients with a preoperative estimated GFR of more than 60 ml · min$^{-1}$ · 1.73 m$^{-2}$ who developed a chronic kidney disease (estimated GFR of 60 ml · min$^{-1}$ · 1.73 m$^{-2}$ or less) until day 90, no statistical difference could be found between the groups (table 4). We want to stress that this is a result of a *post hoc* analysis and not a primary or secondary study endpoint. The issue of a clinical relevance of this finding should therefore be addressed in future studies.

To assess the nephrotoxic side effects of colloids, routine laboratory parameters such as creatinine, estimated GFR, or urea, as well as the RIFLE criteria, have been measured in many previous trials.[2,15] Serum creatinine and the derived GFR calculation by the Cockroft–Gault formula are especially of limited validity in patients with minor decreases in renal function. In contrast, Shlipak *et al.*[21] showed that serum cystatin C was more sensitive for detecting mild renal dysfunction than serum creatinine alone.

The postoperative incidence of pruritus in our patients (HES group = 2.1%; albumin group = 15.1%) was low compared with previous studies. A subgroup analysis of the 6S trial in 295 survivors after severe sepsis demonstrated pruritus incidences of 49% (HES group) and 43% (Ringer group), respectively, without differences between groups.[44] In our study, we observed a significantly higher incidence of pruritus in albumin patients. To the best of our knowledge there are no data in the literature with respect to this unexpected difference, nor are there published pathophysiological or histochemical aspects that would provide an explanation. Certainly the incidence of pruritus was not evaluated in this study preoperatively, and other potential triggers of pruritus were present, such as perioperative intravenous or epidural opioid administration. Conclusively we do not believe at this stage that this reflects a relevant negative effect of albumin.

Our study has some limitations. First, we performed a single blinded study, that is, researchers were blinded for analysis but clinicians were not. The missing blinding of physicians, especially regarding the preoperative renal function, could have influenced the investigation in some ways that would be difficult or impossible to assess. Nevertheless, the protocols for administration of both albumin 5% and HES 6% were identical. Second, power analysis was performed

**Table 4.** Renal Function and Kidney Injury

| | Albumin (N = 53) | *P* Value | HES (N = 47) | *P* Value | *P* Value |
|---|---|---|---|---|---|
| Cystatin C ratio | 1.11 (1.01/1.23) | | 1.08 (1/1.2) | | 0.165 |
| Cystatin C ratio intergroup difference | 0.03 (95% CI: –0.09 to 0.08) | | | | |
| Serum cystatin C, mg/l | | | | | |
| Preoperative | 1.02 (0.82/1.44) | | 1.02 (0.83/1.36) | | 1.000* |
| After surgery | 0.85 (0.7/1.11) | < 0.0001*† | 0.78 (0.65/1.11) | < 0.0001*† | 1.000* |
| POD 1 | 0.91 (0.75/1.12) | 0.0002*† | 0.94 (0.75/1.14) | 0.1066*† | 1.000* |
| POD 3 | 0.82 (0.66/1.15) | < 0.0001*† | 0.82 (0.69/1.06) | 0.0001*† | 1.000* |
| POD 90 | 1.23 (1/1.53) | < 0.0001*† | 1.13 (0.94/1.39) | 1.000*† | 0.885* |
| eGFR decrease until POD 90, % | 11.46 | | 8.96 | | 0.792 |
| Patients with preoperative CKD, n/N (%) | 18/52 (34.6) | | 18/47 (38.3) | | 0.835 |
| Patients with CKD at POD 90, n/N (%) | 23/43 (53.5) | 0.020† | 18/42 (42.9) | 0.180† | 0.388 |
| Patients changing to CKD until POD 90, n/N (%) | 8/42 (19.1) | | 4/43 (9.3) | | 0.228 |
| Serum NGAL, ng/ml | n = 52 | | n = 47 | | |
| Preoperative | 194.6 (135.6/266.4) | | 183.6 (136.2/241.8) | | 1.000* |
| After surgery | 230.5 (177.4/354) | 0.2773*† | 207.4 (152.8/301.8) | 1.000*† | 1.000* |
| 2 to 4 h postoperation | 215.3 (158.3/326.1) | 0.0504*† | 207.2 (156/307) | 1.000*† | 1.000* |
| POD 1 | 208.1 (153.2/318.4) | 1.000*† | 230.8 (162.2/304) | 1.000*† | 1.000* |
| POD 3 | 211.7 (145.3/287.3) | 1.000*† | 176.9 (121.4/247.7) | 1.000*† | 1.000* |
| RIFLE stage POD 3, n (%) | | | | | 1.000 |
| No AKI | 49 (96.1) | | 47 (100) | | |
| Risk | 2 (1) | | 0 (0) | | |
| Injury | 2 (1) | | 0 (0) | | |
| Failure | 0 (0) | | 0 (0) | | |
| RIFLE stage POD 90, n (%) | | | | | 0.586 |
| No AKI | 35 (83.3) | | 38 (88.4) | | |
| Risk | 5 (11.9) | | 5 (11.6) | | |
| Injury | 2 (4.8) | | 0 (0) | | |
| Failure | 0 (0) | | 0 (0) | | |

Metric values are given as median (interquartile range). Mann–Whitney U test was used for metrical variables and Fisher exact test (two sided) for dichotomous variables.

*Data show adjusted *P* values in repeated measurements using Bonferroni correction. †Data show comparison with baseline values.

AKI = acute kidney injury; CKD = chronic kidney disease, defined as glomerular filtration rate less than 60 ml · $min^{-1}$ · 1.73 $m^{-2}$ according to the National Kidney Foundation[39]; eGFR = estimated glomerular filtration rate; HES = hydroxyethyl starch; NGAL = neutrophil gelatinase-associated lipocalin; POD = postoperative day; RIFLE = risk, injury, failure, loss, and end-stage renal disease; SP = study period (preoperative until POD 90).

assuming differences in renal function parameters of at least 20%. Although this number might appear high, it was considered as a clinically significant outcome. Third, our cohort of patients may seem small, but the sample size was determined by an appropriate power analysis. Also we tried to enroll a homogenous study population with patients undergoing cystectomy and a GFR above 30 ml/kg. When analyzing patient characteristics, it turned out that the study groups were well comparable with the exception of a nonsignificant ($P = 0.054$) trend toward higher ASA status in the albumin group. Comparing ASA III and IV patients in a subgroup analysis, we found no significant differences concerning primary and secondary outcome parameters. Fourth, the average volume of colloid infusion until transfer to the intensive care unit or regular ward was significantly higher in the HES group (Δ 363 ml), although hemodynamic parameters were comparable in both groups. In contrast, significantly more crystalloids (Δ 373 ml) were administered in the albumin group during surgical intervention. This can explain why there was no difference in hemodynamic variables despite a slightly higher colloid supply in the HES group. However, volume replacement was triggered by predefined hemodynamic target parameters. Another possible explanation could be the different pharmacokinetics of these two infusion solutions. Both colloids can shift out of the intravascular space, whereas HES can be stored in the reticuloendothelial system. In contrast to albumin, HES can be eliminated continuously *via* the urine.[12,45] The different intravascular half-life of the comparators could also explain, at least in part, the different fluid requirements. Fifth, we measured serum neutrophil gelatinase-associated lipocalin but not urinary neutrophil gelatinase-associated lipocalin to assess kidney injury. The latter is a more sensitive parameter for glomerular damage. The preference of serum determination was due to the surgical procedure of an ileum conduit in 50% of all cases and, hence, the impossibility to collect noncontaminated urinary samples. Finally, the subgroup analyses of intensive care *versus* nonintensive care patients, as well as the incidences of chronic kidney disease, were performed in a *post hoc* fashion, because these had not been defined as primary or secondary endpoints. Hence, the respective results should be considered with caution and therefore cannot be conclusively assessed.

**Table 5.** Comparison of ICU and Non-ICU Patients

| | Albumin (N = 53) | | *P* Value | HES (n = 47) | | *P* Value |
|---|---|---|---|---|---|---|
| | ICU 47.2% (N = 25) | Non-ICU 52.8% (N = 28) | | ICU 48.9% (N = 24) | Non-ICU 51.1% (N = 23) | 0.841* |
| Crystalloid requirements, ml | | | | | | |
| Total crystalloid requirements during SP | 11,489 ± 2,806 | 10,363 ± 2,177 | 0.209 | 12,052 ± 2884 | 10,139 ± 2,490 | 0.019 |
| Until transfer to ICU, PACU, or regular ward | 3,244 ± 1,347 | 3,404 ± 890 | 0.247 | 2,807 ± 793 | 3,109 ± 1,252 | 0.567 |
| From transfer to POD 1 | 3,071 ± 1,232 | 2,348 ± 933 | 0.048 | 3,346 ± 1,591 | 2,459 ± 1,097 | 0.012 |
| From POD 1 to 3 | 5,175 ± 1,707 | 4,611 ± 1,691 | 0.314 | 5,900 ± 2,134 | 4,572 ± 1,534 | 0.009 |
| Colloid requirements, ml | | | | | | |
| Total colloid requirements during SP | 2,080 ± 971 | 1,370 ± 635 | 0.004 | 2,308 ± 1,087 | 1,678 ± 719 | 0.038 |
| Until transfer to ICU, PACU, or regular ward | 1,850 ± 692 | 1,334 ± 588 | 0.008 | 2,192 ± 861 | 1,678 ± 719 | 0.040 |
| From transfer to POD 1 | 230 ± 420 | 36 ± 131 | 0.036 | 117 ± 416 | 0 ± 0 | 0.043 |
| From POD 1 to 3 | 0 ± 0 | 0 ± 0 | 1.000 | 0 ± 0 | 0 ± 0 | 1.000 |
| Transfusion rates, n (%) | | | | | | |
| Total transfusion rates during SP | | | | | | |
| Erythrocyte | 15 (60) | 7 (25) | 0.013 | 15 (62.5) | 2 (8.7) | < 0.0001 |
| Fresh-frozen plasma | 8 (32) | 0 (0) | 0.001 | 3 (12.5) | 0 (0) | 0.234 |
| Platelet | 1 (4) | 0 (0) | 0.472 | 0 (0) | 0 (0) | – |
| Intraoperative | | | | | | |
| Erythrocyte | 12 (48) | 5 (17.9) | 0.037 | 9 (37.5) | 2 (8.7) | 0.036 |
| Fresh-frozen plasma | 7 (28) | 0 (0) | 0.003 | 3 (12.5) | 0 (0) | 0.234 |
| Platelet | 0 (0) | 0 (0) | – | 0 (0) | 0 (0) | – |
| Until POD 1 | | | | | | |
| Erythrocyte | 7 (28) | 2 (7.1) | 0.067 | 8 (33.3) | 0 (0) | 0.004 |
| Fresh-frozen plasma | 2 (8) | 0 (0) | 0.218 | 0 (0) | 0 (0) | – |
| Platelet | 1 (4) | 0 (0) | 0.472 | 0 (0) | 0 (0) | – |
| Until POD 3 | | | | | | |
| Erythrocyte | 4 (16) | 1 (3.6) | 0.176 | 4 (16.7) | 0 (0) | 0.109 |
| Fresh-frozen plasma | 0 (0) | 0 (0) | – | 0 (0) | 0 (0) | – |
| Platelet | 0 (0) | 0 (0) | – | 0 (0) | 0 (0) | – |
| Maximum norepinephrine, $\mu g \cdot kg^{-1} \cdot min^{-1}$ | | | | | | |
| Intraoperative | 0.18 ± 0.08 | 0.14 ± 0.07 | 0.031 | 0.19 ± 0.1 | 0.13 ± 0.06 | 0.057 |
| POD 1 | 0.08 ± 0.11 | 0 ± 0 | < 0.0001 | 0.08 ± 0.1 | 0 ± 0 | < 0.0001 |
| POD 3 | 0.01 ± 0.03 | 0 ± 0 | 0.259 | 0.02 ± 0.06 | 0 ± 0 | 0.022 |
| Need for norepinephrine, n (%) | | | | | | |
| Intraoperative | 25 (100) | 28 (100) | – | 24 (100) | 23 (100) | – |
| POD 1 | 14 (56) | 0 (0) | < 0.0001 | 13 (54.2) | 0 (0) | < 0.0001 |
| POD 3 | 3 (12) | 0 (0) | 0.218 | 5 (20.8) | 0 (0) | 0.050 |
| Need for vasopressin, n (%) | | | | | | |
| Intraoperative | 0 (0) | 0 (0) | – | 1 (4.2) | 1 (4.3) | 1.000 |
| POD 1 | 1 (4) | 0 (0) | 0.472 | 1 (4.2) | 0 (0) | 1.000 |
| POD 3 | 0 (0) | 0 (0) | – | 1 (4.2) | 0 (0) | 1.000 |
| Need for epinephrine, n (%) | | | | | | |
| Intraoperative | 2 (8) | 0 (0) | 0.218 | 1 (4.2) | 0 (0) | 0.609 |
| POD 1 | 1 (4) | 0 (0) | 0.472 | 2 (8.3) | 0 (0) | 0.489 |
| POD 3 | 0 (0) | 0 (0) | – | 1 (4.2) | 0 (0) | 1.000 |
| Need for dobutamine, n (%) | | | | | | |
| Intraoperative | 3 (12) | 1 (3.6) | 0.333 | 1 (4.2) | 1 (4.3) | 1.000 |
| POD 1 | 1 (4) | 0 (0) | 0.472 | 0 (0) | 0 (0) | – |
| POD 3 | 0 (0) | 0 (0) | – | 0 (0) | 0 (0) | – |

Metric values are given as mean ± SD. Crystalloid requirement is up to POD 3 and colloid requirements without erythrocyte, fresh-frozen plasma, and platelet transfusion. Mann–Whitney U test was used for metrical variables and Fisher exact test (two sided) for dichotomous variables.

*Data compare ICU transfer rates in both groups.

ICU = intensive care unit; PACU = postanesthesia care unit; POD = postoperative day; SP = study period.

In conclusion, this randomized, controlled, single-center trial did not reveal significant differences concerning the influences of a balanced 6% HES (130/0.4) or an albumin 5% solution on global renal function and parameters of kidney injury in noncritical ill patients receiving major surgery. Our investigation indicates that perioperative 5% albumin

and balanced 6% HES solutions have comparable safety profiles with respect to renal function in these patients.

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## Competing Interests

The authors declare no competing interests.

## Reproducible Science

Full protocol available at: tobias.kammerer@med.uni-muenchen.de. Raw data available at: tobias.kammerer@med.uni-muenchen.de.

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