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Hydroxyethyl Starch and Acute Kidney Injury in Orthotopic Liver Transplantation: A Single-Center Retrospective Review

William R Hand, MD,

Department of Anesthesia & Perioperative Medicine, Medical University of South Carolina, Charleston, South Carolina

Joseph R Whiteley, DO,

Department of Anesthesia & Perioperative Medicine, Medical University of South Carolina, Charleston, South Carolina

Tom I Epperson, MD,

Department of Anesthesia & Perioperative Medicine, Medical University of South Carolina, Charleston, South Carolina

Lauren Tam, BS,

Georgetown University School of Medicine, Washington, DC

Heather Crego, RN, BSN, CCTC,

Medical University of South Carolina, Medical University of South Carolina, Charleston, South Carolina

Corresponding Author: William R Hand, MD, Department of Anesthesia & Perioperative Medicine, Medical University of South Carolina, 167 Ashley Avenue, Suite 301, Charleston, South Carolina 29425, 843-792-5442, 843-792-9314 (fax), handw@musc.edu.

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DISCLOSURES:

Name: William R Hand, MD

Contribution: Design, Data Acquisition, Analysis, Manuscript, Corresponding Author

Attestation: Author has seen the original study data, reviewed the analysis of the data, approved the final manuscript, and is the author responsible for archiving the study files

Name: Joseph R Whiteley, DO

Contribution: Design, Data Acquisition, Analysis, Manuscript

Attestation: Author has seen the original study data, reviewed the analysis of the data, and approved the final manuscript **Name:** Tom I Epperson, MD

Contribution: Analysis, Manuscript

Attestation: Author has seen the original study data, reviewed the analysis of the data, and approved the final manuscript

Name: Lauren Tam, BS

Contribution: Data Acquisition, Analysis, Manuscript

Attestation: Author has seen the original study data, reviewed the analysis of the data, and approved the final manuscript

Name: Heather Crego, RN, BSN, CCTC

Contribution: Data Acquisition, Manuscript

Attestation: Author has seen the original study data, reviewed the analysis of the data, and approved the final manuscript

Name: Bethany Wolf, PhD

Contribution: Statistical Analysis, Manuscript revision

Attestation: Author has seen the original study data, reviewed the analysis of the data, and approved the final manuscript

Name: Kenneth D Chavin, MD, PhD

Contribution: Manuscript

Attestation: Author has seen the original study data, reviewed the analysis of the data, and approved the final manuscript

Name: David J Taber, PharmD

Contribution: Design, Data Acquisition, Analysis, Manuscript

Attestation: Author has seen the original study data, reviewed the analysis of the data, and approved the final manuscript

This manuscript was handled by: Avery Tung, MD

Bethany Wolf, PhD,

Department of Public Health Sciences, Medical University of South Carolina, Charleston, South Carolina

Kenneth D Chavin, MD, PhD, and

Division of Transplant Surgery, Medical University of South Carolina, Charleston, South Carolina

David J Taber, PharmD

Division of Transplant Surgery, Medical University of South Carolina, Charleston, South Carolina

Abstract

Background—Acute kidney Injury (AKI) is a frequent complication of orthotopic liver transplantation (OLT). Hepatic failure pathophysiology and intraoperative events contribute to AKI after OLT. Colloids are routinely used to maintain intravascular volume during OLT. Recent evidence has implicated 6% hydroxyethyl starch (HES) (130/0.4) with AKI in critically ill patients.

Methods—We performed a retrospective cross-sectional analysis of electronic anesthesia records, surgical dictations, and perioperative lab results. Postoperative AKI incidence was determined by RIFLE (**R**isk **I**njury **F**ailure **L**oss **E**nd-Stage) criteria. AKI was staged into Risk, Injury, and Failure based on change in serum creatinine from preoperative baseline to peak level by postoperative day 7. Uni- and multivariate analysis was used to evaluate the association between type of intraoperative colloid administered and AKI.

Results—One hundred seventy-four adult patients underwent OLT and had complete records for review. Of these, 50 received only 5% albumin, 25 received both 5% albumin and HES, and 99 received only HES. Albumin only, albumin and HES, and HES only groups were otherwise homogenous based on patient characteristics and intraoperative variables. There was a statistically significant linear by linear association between type of colloid(s) administered and AKI (Rifle Criteria – Injury Stage). Patients administered HES were 3 times more likely to develop AKI within 7 days after OLT as compared to albumin (adjusted odds ratio 2.94, 95% CI: 1.13-7.7, $p=0.027$). The linear trend between colloidal use (5% albumin only vs. albumin/HES vs. HES only, ranked ordering) and “Injury” was statistically significant ($p=0.048$). A propensity-matched analysis also showed a significant difference in incidence of AKI between the patients receiving albumin compared with HES ($p=0.044$).

Conclusions—Patients receiving 6% HES (130/0.4) likely had an increased odds of AKI as compared to patients receiving 5% albumin during OLT. These retrospective findings are consistent with recent clinical trials that found an association between 6% HES (130/0.4) and renal injury in critically ill patients.

Introduction

Acute kidney injury (AKI) after orthotopic liver transplantation (OLT) is a common complication, with reported incidences ranging from 17% to 95%.¹ The wide variability in reported AKI incidence after OLT is attributable in part to lack of a consensus definition for AKI.² To address this issue, the Acute Dialysis Quality Initiative Group developed a consensus definition and classification system for AKI identified by the acronym RIFLE

(Risk, Injury, Failure, Loss, and End Stage) that specifies the degree and duration of renal dysfunction. This classification system is based on changes in serum creatinine (or glomerular filtration rate) and/or changes in urine output.³ The RIFLE classification system has been validated as an outcome predictor, with worsening RIFLE class being associated with a progressive increase in mortality.⁴ In patients undergoing OLT, both RIFLE criteria class Injury and Failure result in increased length of hospitalization and in the case of Failure, increased mortality.⁵

The etiology of AKI after OLT is multifactorial. End-stage liver disease (ESLD) results in a hyperdynamic circulatory syndrome characterized by peripheral vasodilation, hypotension, and high cardiac output.⁶ Arterial hypotension and splanchnic vasodilation predispose to renal dysfunction through renal circulatory vasoconstriction and hypoperfusion.⁷ Perioperative risk factors associated with AKI after OLT include blood transfusion, intra- and postoperative hypotension, preoperative hypertension, elevated bilirubin levels, alcoholic cirrhosis, and length of surgery.⁸⁻¹¹

The choice of fluid resuscitation in patients with ESLD may also play a role in AKI. Because hypoalbuminemia and low oncotic pressure cause IV fluids to diffuse into the interstitium, albumin has been the fluid of choice for intravascular volume resuscitation in liver transplantation at many centers. Albumin is a more potent plasma expander than crystalloid and has antioxidant and antiinflammatory properties.^{12,13} Albumin has also reduced renal impairment in patients with cirrhosis and spontaneous bacterial peritonitis.¹⁴ Despite these observations, however, the Saline versus Albumin Fluid Evaluation Study, which compared the use of albumin to normal saline, demonstrated no difference in mortality and renal replacement therapy (RRT) in a large heterogeneous intensive care unit (ICU) population.¹⁵

Increasingly, evidence suggests that 6% hydroxyethyl starch (130/0.4) (henceforth referred to as HES) causes renal injury. The Crystalloid versus Hydroxyethyl Starch Trial (CHEST) prospectively randomized 7,000 patients to hetastarch or normal saline and found a 21% relative (1.2% absolute) increase in need for RRT in patients receiving HES.¹⁶ A Dutch trial of 800 ICU patients with severe sepsis likewise found an increased likelihood of RRT in patients receiving HES versus Ringer's acetate solution.¹⁷ These studies led the Food and Drug Administration to issue a warning in November of 2013 that HES use increases the risk of mortality and renal injury requiring RRT in critically ill adult patients.¹⁸⁻²⁰

At the study institution, the decision to deliver colloid to a transplant recipient is protocol driven. A team of anesthesiologists (5) use arterial-waveform analysis in addition to standard monitors to estimate fluid-responsive hypotension and measure recipient colloid oncotic pressure. The team limits crystalloid administration and empirically administers colloid for fluid deficits unless blood-component transfusion is indicated. Additionally, colloids are administered for large volume ascites drainage, consistent with large volume paracentesis therapy. The choice of which colloid to administer (albumin vs. HES) was optional until 2011, when the hospital's Pharmacy and Therapeutics Committee decided to exclude albumin from operative cases (including OLTs) after analyzing the literature regarding the safety and efficacy of HES and considering the price advantage. This

retrospective study was designed to explore the hypothesis that the type of colloid administered during OLT is associated with AKI.

Methods

We obtained IRB approval to retrospectively query our computerized medical record system for all cases with CPT code 47135 (liver allotransplantation). Our electronic anesthesia medical record system (PICIS, Wakefield, MA) and operative dictation reports were reviewed for the following data points: colloid usage (5% albumin or HES), vital signs (mean arterial blood pressure [MAP], central venous pressure [CVP]), blood product transfusion, administration of recombinant factor VIIa, intraoperative use of vasoactive substances (drug and dose), surgery duration, estimated blood loss, and basic demographics. For each patient, we also identified Model for End-Stage Liver Disease (MELD) score, serial serum creatinine and electrolyte values, need for RRT, postoperative complications (thrombus requiring reoperation, biliary leak, or early graft failure), mortality (intraoperative and 30-day), and severity of illness upon admission. The University Health System Consortium (UHC), in which our hospital participates, calculates a severity of illness for every patient admitted based on the APR-DRG (All Patient Refined Diagnosis Related Groups, 3M Health Information Systems). Severity is calculated using a combination of patient demographics, coded comorbidities, principal and secondary diagnoses and procedures to define different levels of severity and complexity of treatment. The query examined all available records within our operating room electronic health record system (2010-2013). The authors acknowledge including only the patient records since the institution of the electronic medical record limits the sample size; however, the quality of data on a sample of paper records for liver transplantation was inadequate for collection and reliable analysis.

The primary outcome of interest was presence of postoperative AKI which was determined using the RIFLE "Injury" criteria of doubling serum creatinine (50% decreased glomerular filtration rate) within 7 days of surgery.³ The primary comparison of interest was to determine whether use of HES or 5% human albumin was associated with the development of AKI. All patients were assigned to 1 of 3 groups based on type of colloid administered intraoperatively: (1) those who received albumin only, (2) those who received albumin and HES, and (3) those who received HES only. Grouping patients in this context provided an ordered ranked assignment, allowing the investigators to conduct both categorical comparisons and tests for linear trends for each outcome variable of interest. The associations among the 3 colloid groups with red blood cell (RBC) and fresh frozen plasma transfusion volume, presence of thrombosis, change in serum creatinine levels, and total colloid volume were examined using one-way ANOVA. Associations between colloid group and categorical variables were examined using Chi-Square and Fisher's Exact tests when appropriate. We also tested for rank linear trends by colloid group using the Mantel-Haenszel linear-by-linear test for association.

Patients were defined by RIFLE AKI criteria as having: no "Risk," "at Risk," "Injury," or "Failure." By definition, any patient qualifying for a classification would also meet or exceed the criteria for lesser classes. For the multivariate analysis, patients were

dichotomized as those with “Injury” or “Failure” versus no “Risk” or at “Risk.” Multivariate logistic regression models of the primary outcome (AKI) were constructed to test the association with colloid type controlling for severity of illness, MELD score, intraoperative hemodynamics (MAP and CVP), baseline characteristics and interaction terms.

A propensity score matching analysis was also performed to adjust intergroup differences between subjects given albumin only and subjects given HES only due to potential selection bias in the decision to give albumin versus HES. Propensity scores were estimated using a logistic regression model with treatment assignment as the dependent variable and all identifiable confounding variables as independent covariates. Potential confounding variables were defined as those having a p-value <0.2 in univariate tests of association with colloid type and/or AKI. Patients in the 2 groups were matched based in their propensity scores using the nearest neighbor approach with replacement and 2-to-1 matching for HES only to albumin only. The maximum difference of propensity score for a match was 0.2 standard deviations of the logit of the propensity score. Sample balance was estimated post-matching using the weighted standardized difference.²¹ Propensity score analysis was conducted using the Matching Package in R v.3.0.2.^{22,23} All other analyses were conducted in SPSS v21.0 (IBM Corp. Armonk, NY).

Results

We identified 230 OLTs in our electronic medical record. Of these patients, 174 met our criteria for analysis. Thirty-five patients were excluded for the following reasons: simultaneous dual-organ (liver and kidney) transplant (19), pediatric recipient (8), and incomplete “critical” data (preoperative labs or dictations) (8). An additional 21 patients did not receive any colloid (or none was documented). The final cohort included 168 unique subjects and 174 procedures. Patients were divided into 3 groups based on the type(s) of colloid administered during surgery: 5% albumin, HES, or both. Fifty (28.7%) of the study patients received 5% albumin only (control cohort), 99 (56.9%) received HES only (high risk cohort), and 25 (14.4%) received both colloids (moderate risk cohort).

Univariate Analysis Results

Baseline characteristics for the study population are shown in Table 1. The mean age of all study participants at date of transplant was 55 + 10 years with a median age = 57. Mean age did not vary significantly among groups. A majority of subjects were male in both groups. The causes of liver failure were evenly distributed among the 3 groups. There were no differences in distribution of patients with minor or moderate severity of illness. However, the distributions of patients with major or extreme severity of illness were significantly different among the cohorts, with more patients with the highest illness acuity (extreme) receiving albumin and more of those with major severity of illness receiving HES (p=0.003).

Intraoperative characteristics of the groups based on type of colloid(s) received are shown in Table 2. The mean volumes of colloids administered by group are shown in Table 2. The HES only group received 81% more HES than the albumin and HES group (740mL vs 1342mL). Mean MELD scores (at the time of transplant with exception points included) were nearly identical among all 3 groups (22±5 vs. 22±4 vs. 21±5, p=0.127, respectively).

The individual MELD components are shown with ranges among the 3 groups: serum creatinine 1.1-1.2mg/dL ($p>0.80$), international normalized ratio 1.6-1.7 ($p>0.93$), serum bilirubin 5.0-8.2mg/dL ($p>0.129$). Surgical durations were similar among the groups as were the blood pressure values (mean CVP and MAP). Estimated blood loss was larger in the albumin only group ($p=0.049$). There were no differences in administration of vasoactive drugs or antifibrinolytic drug administration. With the exception of platelet use, blood product administration was similar among the groups with a mean RBC requirement of 2342 mL for the entire cohort. Blood product usage among the albumin only, both colloids and HES only cohorts was as follows: RBCs: 2706 ± 2449 mL versus 3059 ± 3714 versus 2042 ± 2276 , respectively; $p=0.123$; fresh frozen plasma: 2424 ± 1870 versus 2823 ± 2934 versus 2072 ± 2224 , respectively; $p=0.287$; platelets: 427 ± 480 versus 472 ± 791 versus 248 ± 394 , respectively; $p=0.037$. Neither the administration of intraoperative platelets nor the volume of platelets transfused was associated with the development of AKI “Injury” ($p=0.76$ and 0.94 , respectively). The presence of ascites before transplantation across the entire study cohort was 43.2%. The proportion of ascites presence ranged among the 3 groups from 36% (HES only) to 53% (albumin) ($p=0.14$). Preoperative ascites was not associated with AKI regardless of colloid group.

Postoperative outcomes are displayed in Table 3. Other than AKI, there were no associations between type of colloid(s) administered and any reported postoperative complication. There was also no appreciable difference in ICU or hospital length of stay. No patients included in the analysis required dialysis preoperatively (all dual organ transplants were excluded). As mentioned above, AKI was assessed in terms of changes in serum creatinine values and classified kidney damage by RIFLE Criteria.³ The “Risk” group constituted patients with a 50% increase in serum creatinine from baseline, whereas the “Injury” group required at least a doubling of the baseline creatinine and “Failure” group at least tripling in serum creatinine or receiving posttransplant dialysis. There were no statistically significant differences in the percentage of patients meeting these criteria. The HES only group had the highest percentage of patients in all 3 AKI stages, followed by the combination 5% albumin/HES group, while the 5% albumin only group demonstrated the lowest incidence of each stage of AKI.

Results of Linear by Linear and Multivariate Analyses

The linear association between colloidal use (5% albumin only vs albumin/HES vs HES only, ranked ordering) and “Injury” was statistically significant ($p=0.048$). There was not a significant linear trend of increasing odds of either “Risk” or “Failure” by colloid use ($p=0.221$ and 0.622 , respectively, Figure 1). Eighteen patients required RRT (continuous venous-venous hemodialysis or interval hemodialysis) within 30 days of transplant. There was no correlation among the 3 cohorts and the need for dialysis or the need for RRT. The only 2 deaths by 30-days posttransplant were in the HES group (2.0%), however the scarcity of mortality in the entire cohort precluded the determination of any statistical associations between HES use and death.

Table 4 displays a multivariate logistic regression model of AKI (“no risk” or “at risk” versus “injury” or “failure”), demonstrating that after controlling for baseline differences

among groups, patients receiving only HES had significantly increased odds of developing AKI “Injury” as compared to those receiving only 5% albumin (adjusted odds ratio 2.94, 95% CI: 1.13-7.7, $p=0.027$). Severity of illness, blood product administration, and mean CVP (corollary of volume status) were not associated with AKI.

Table 5 displays a second multivariate logistic regression model for AKI. In this model, HES use for each subject was redefined as none, < 500 mL HES, or > 500 mL HES, mean intraoperative CVP was redefined as an ordinal variable and intraoperative blood loss was included in the model. The results demonstrate similar trends in association between the dependent outcomes and independent covariates, when compared to the continuous variable multivariate model (Table 4). Patients who received more than 500 mL of HES, as compared to those receiving only intraoperative albumin, showed a trend toward developing AKI “Injury” that approached statistical significance ($p=0.059$) after controlling for severity of illness, CVP and blood loss. Smaller amounts of intraoperative HES did not show an increased risk of AKI “Injury,” (odds ratio 2.39, $p=0.190$).

Results of Propensity Score Analysis

Variables selected for inclusion in the propensity score model included severity of illness at admission, MELD score, and non-alcoholic steatohepatitis (NASH) cirrhosis as the primary reason for liver failure. Comparable patient groups included 37 patients who received albumin only and 74 patients who received HES only. Baseline characteristics and the weighted standardized mean difference between the 2 groups of the complete sample and of the propensity matched sample are shown in Table 6. Similar to the multivariate model in Table 4, there was a significant difference in the propensity matched sample in AKI incidence between subjects treated with albumin only compared to subjects treated with HES only ($p = 0.044$). In matched data, patients treated with HES had increased odds (1.18) of AKI compared to patients given albumin only (95% CI: 1.01-1.39).

Discussion

This retrospective longitudinal cohort study demonstrates the benefit of continual quality assessment and improvement efforts by multidisciplinary clinical care teams. This project originated from an internal observation of increased AKI in OLT recipients after changing the type of colloid used from 5% albumin to HES in 2011. This change in practice was encouraged as a cost-savings in light of literature suggesting no difference in renal outcomes between patients randomized to receive either 5% albumin or 6% HES.²⁴ In contrast, our results suggest that HES likely is associated with AKI; supported by the statistically significant linear by linear association between the type of colloid(s) administered and incidence of AKI by RIFLE “Injury” classification. The data presented above caused our interdisciplinary team to revert to exclusively using albumin during OLT for colloidal volume expansion. Use of HES in the perioperative setting has been cautioned within our institution, awaiting validation of its safety.

The 3 compared colloid groups (albumin only, HES/albumin, and HES only) had similar demographics, causes of liver failure, and MELD scores. Within the limits of retrospective analysis, there does not appear to be a confounding variable associated with AKI that was

disproportionately present within either of the HES groups. In fact, patients in the albumin only group were more likely to be admitted with an APR-DRG classification of extreme severity of illness. Our measured surrogates for ischemia and hypoperfusion included: length of surgery, mean MAP, CVP, estimated blood loss, and RBC transfusion requirement. These findings did not differ among colloid groups, indicating that the HES group did not undergo more complicated surgery or require more blood transfusions. Additionally, vasopressor use, antifibrinolytic use, and bilirubin levels were similar within all 3 colloid groups. The fundamental basis of the linear-by-linear association analysis was grounded on the assumption that an increased volume of HES administration would create a ranking risk of AKI. This assumption was feasible because the volume of HES administered in the HES only group was nearly twice that in the Albumin and HES group, while patients in the Albumin only group did not receive any HES. This finding is consistent with the dose-effect relationship between HES administration and AKI shown by Brunkhorst et al.²⁵ Our results cannot comment on the safety of relatively low volume HES administration within the OLT populations as has been demonstrated within the general critical care population because the average volumes of HES administered in both HES groups exceeded “low threshold” definitions for immediate resuscitation (HES volumes in HES and Albumin and HES-only cohorts: 740 ± 702 mL and 1342 ± 570 mL).²⁶

Our retrospective review could not *a priori* control for confounding variables and thus required the use of multivariate analysis for HES induced AKI. When the multivariate analysis included covariates in a continuous fashion, patients who received HES had significantly higher odds of developing AKI. When covariates were included in a transformed categorical ranked analysis, this trend continued but did not reach statistical significance ($p=0.059$). This discrepancy may have been due to converting variables from continuous to categorical form, which reduced the ability of the model to detect differences, or because our categories for HES volume (none, <500 mL, >500 mL) were not optimally defined. We categorized HES by discrete volume increments (rather than continuously) because nearly all patients received HES in 500 mL. A few patients received less than 500 mL, but almost no patients received doses larger than 500 mL that were not in multiples of 500 mL.

The propensity analysis described above and shown in Table 6 further demonstrates that confounding covariates did not appreciably influence the impact of colloid type on the incidence of AKI. No model could be developed for the decision to administer HES instead of albumin because that decision was largely made by hospital administration, and therefore unlikely to be confounded by pathophysiologic factors which may, coincidentally, also affect AKI. As an example, thrombocytopenia might have caused the anesthesiologist to administer albumin instead of HES due to fear of subtle platelet dysfunction associated with HES. We found, however, that platelet use did not differ among categories of HES use.

Because of our relatively small sample size, we were unable to demonstrate an association between HES and the need for RRT in OLT. While recent literature suggests an association between renal failure and HES use in septic patients, the association in OLT patients may be different in magnitude. In light of the recent Food and Drug Administration warning, a prospective randomized trial comparing HES to albumin in OLT may not be feasible.¹⁸⁻²⁰

However, future large-scale multicenter analyses, using retrospective or registry data may better define the risk of AKI associated with these products in OLT patients.

Conclusion

Our research likely shows a retrospective linear by linear trend between 6% HES (130/0.4) administration in OLT and RIFLE “Injury” stage AKI. Clinicians managing patients undergoing high-risk surgery or in critical condition should consider alternative colloids to 6% HES (130/0.4) until more definitive evidence is published.

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Figure 1.

The percent of patients that developed of acute kidney injury by the three designated RIFLE criteria (at risk, injury and failure) based on intra-operative colloidal agent type. Liver transplant patients that received intraoperative albumin for colloidal fluid support were less likely to develop acute kidney injury. There was a linear association ($p=0.048$) between colloidal use and development of AKI. After adjusting for baseline confounding variables, patients that received HES were nearly three times more likely to develop AKI compared to those that received albumin (Adjusted Hazard Ratio 2.97, 95% CI: 1.13 – 7.7, $p=0.027$). RIFLE= risk, injury, failure, loss, end stage disease, HES= hydroxyethyl starch, AKI= acute kidney injury

Table 1

Comparison of baseline demographics and transplant characteristics among groups

Baseline Characteristics	Albumin Only (n=50)	Albumin and HES (n=25)	HES Only (n=99)	p-Value
Mean Age (yrs) $\pm$ SD	55 $\pm$ 10	53 $\pm$ 11	56 $\pm$ 10	0.279
Gender				
Female	28%	44%	38%	0.314
Male	72%	56%	62%	
African-American	16%	20%	11%	0.461
Cause(s) of Liver Failure				
Hepatitis C	38%	48%	44%	0.673
EtOH	22%	12%	22%	0.502
NASH	20%	8%	13%	0.333
HCC	26%	28%	19%	0.515
Fulminant	4%	0%	1%	0.326
MELD at Time of Transplant	22 $\pm$ 5	22 $\pm$ 4	21 $\pm$ 5	0.127
Admit Severity of Illness				
Extreme	22%	16%	7%	0.003*
Major	28%	40%	48%	
Moderate	36%	32%	38%	
Minor	4%	12%	7%	

Characteristics of patients grouped by type of colloid administered during OLT.

* The admission severity of illness distribution was significantly different between groups, with the albumin group having a higher percentage of patients in the highest illness acuity (extreme), as compared with the other two groups (22% vs. 16% vs. 7%, respectively; 4x3 Chi-Squared). HES= hydroxyethyl starch, EtOH= alcohol, NASH= nonalcoholic steatohepatitis, HCC= hepatocellular carcinoma, MELD= model for end stage liver disease; SD = standard deviation

Table 2

Comparison of intra-operative characteristics between groups

Intraoperative Characteristics	Albumin Only (n=50)	Albumin and HES (n=25)	HES Only (n=99)	p-Value
Volume Colloid infused (mean $\pm$ SD) mL	1162 $\pm$ 680	740 $\pm$ 702 + 1180 $\pm$ 663	1342 $\pm$ 570	0.003*
Mean Intraoperative CVP (mmHg $\pm$ SD)	9.9 $\pm$ 4.8	9.3 $\pm$ 2.6	8.3 $\pm$ 3.6	0.053
Mean Intraoperative MAP (mmHg $\pm$ SD)	77 $\pm$ 9	77 $\pm$ 7	76 $\pm$ 7	0.756
Surgery Duration (mean hrs $\pm$ SD)	6.3 $\pm$ 1.5	6.6 $\pm$ 1.8	6.2 $\pm$ 1.6	0.582
Estimated Blood Loss (mL $\pm$ SD)	7,011 $\pm$ 9,887	2,239 $\pm$ 2,998	3,525 $\pm$ 10,044	0.049
Pre-Transplant Labs				
Fibrinogen (mg/dL $\pm$ SD)	212 $\pm$ 89	228 $\pm$ 113	230 $\pm$ 92	0.530
Creatinine (mg/dL $\pm$ SD)	1.2 $\pm$ 0.7	1.1 $\pm$ 0.4	1.1 $\pm$ 0.8	0.800
Total Bilirubin (mg/dL $\pm$ SD)	6.8 $\pm$ 9.0	8.2 $\pm$ 9.3	5.0 $\pm$ 6.2	0.129
INR (ratio $\pm$ SD)	1.7 $\pm$ 0.4	1.6 $\pm$ 0.5	1.7 $\pm$ 0.5	0.930
Intraoperative Aminocaproic Acid Use	70%	72%	79%	0.372
Intraoperative Vasopressin Use	28%	36%	22%	0.342
Intraoperative Octreotide Use	24%	32%	33%	0.497
Intraoperative Vasopressors Use	76%	84%	88%	0.122
Blood Products (% receiving)				
RBCs	90%	92%	87%	0.715
FFP	86%	84%	89%	0.760
Platelets	70%	64%	46%	0.011
Activated Factor VIIa	8%	16%	4%	0.101

Characteristics of intraoperative values and drugs administered. Blood products are reported categorically.

* Significant difference is volume of combined colloids compared to both albumin only and HES only groups. HES= hydroxyethyl starch, CVP= central venous pressure, MAP= mean arterial pressure, RBCs= red blood cells, FFP= fresh frozen plasma, SD = standard deviation

Table 3

Post-operative outcomes

Post-Operative Outcomes	Albumin Only (n=50)	Albumin and HES (n=25)	HES Only (n=99)	Categorical association p-Value	Linear by Linear Association p-Value
Hepatic Artery Thrombosis	4%	4%	5%	0.948	0.760
Portal Vein Thrombosis	0%	0%	2%	0.465	0.248
Mean ICU Days	2.3 ± 2.0	2.7 ± 2.3	2.5 ± 5.3	0.916	N/A
Mean Total Hospital Days	8.1 ± 6.9	8.1 ± 6.4	7.7 ± 8.8	0.958	N/A
Observed Direct Costs	\$84,929 ± \$38,186	\$94,684 ± \$27,014	\$97,871 ± \$33,320	0.107	N/A
AKI by RIFLE Criteria					
At Risk	50%	56%	61%	0.469	0.221
Injury	22%	32%	38%	0.139	0.048
Failure	14%	16%	17%	0.884	0.622
Intraoperative Death	0%	0%	1%	0.683	0.415
30-Day Mortality	0%	0%	2%	0.465	0.248

Characteristics of complications and postoperative outcomes. Linear by Linear Associations based on ranked trend and Categorical associations amongst the three colloid cohorts. HES= hydroxyethyl starch, ICU= intensive care unit, AKI= acute kidney injury, RIFLE= risk, injury, failure, loss, end-stage disease, SD = standard deviation

Table 4

Multivariate model for the dependent variable of acute kidney injury

Covariate*	Adjusted Odds Ratio	95% Confidence Interval	p-Value
Intraoperative Colloidal Use			
Received Albumin	Reference	Reference	Reference
Received Albumin and HES	1.77	0.55–5.7	0.340
Received HES	2.94	1.13–7.7	0.027
Admission Severity of Illness			
Minor	Reference	Reference	Reference
Moderate	0.38	0.03–5.5	0.475
Major	0.75	0.04–13.9	0.846
Extreme	0.30	0.02–4.3	0.376
Mean Intraoperative CVP	1.08	0.98–1.18	0.108
Intraoperative Estimated Blood Loss	1.00	1.00–1.00	0.685
Given Intraoperative Platelets	1.05	0.50–2.2	0.889

Multivariate models evaluating association of variables with incidence of AKI comparing to reference range of Albumin only group. All three groups were similar for available risk factors for AKI except choice of colloid.

* Interaction terms between colloidal use and severity of illness, CVP, and platelet administration were all statistically insignificant ($p > 0.500$). HES= hydroxyethyl starch, CVP= central venous pressure, SD = standard deviation

Table 5

Multivariate model for the dependent variable of acute kidney injury with variables transformed into categories

Covariate *	Adjusted Odds-Ratio	95% Confidence Interval	p-Value
Intraoperative Colloidal Use			
Received Only Albumin	Reference	Reference	Reference
Received 500 mL HES	2.39	0.65 –8.76	0.190
Received >500 mL HES	2.44	0.97 –6.13	0.059
Admission Severity of Illness			
Minor	Reference	Reference	Reference
Moderate	0.38	0.03 –5.5	0.475
Major	0.75	0.04 –13.9	0.846
Extreme	0.30	0.02 –4.3	0.376
Mean Intraoperative CVP			
<6 mmHg	Reference	Reference	Reference
6-8 mmHg	2.44	0.68 –8.71	0.171
9-12 mmHg	2.73	0.78 –9.51	0.115
>12 mmHg	1.73	0.38 –7.85	0.476
Intraoperative Estimated Blood Loss			
1000 mL	Reference	Reference	Reference
1000-2000 mL	0.76	0.23 –2.60	0.667
>2000 mL	0.94	0.45 – 1.95	0.858
Given Intraoperative Platelets	1.05	0.50 –2.2	0.889
Used Cell Saver Intraoperatively	0.49	0.14 –1.8	0.278

* Interaction terms between colloidal use and severity of illness, CVP, platelets and cell-saver were all statistically insignificant ($p > 0.500$) HES= hydroxyethyl starch, CVP= central venous pressure

Table 6

Baseline characteristics of patients receiving albumin or HES only before and after propensity score matching.

	Pre-Matching			Post-Matching		
	Albumin Only (n=50)	HES Only (n=99)	Standardized Difference	Albumin Only (n=37)	HES Only (n=74)	Weighted Standardized Difference
Demographics						
Age (yrs) + SD	55.2 (9.1)	56.4 (10.0)	0.133	55.1 (12.3)	56.2 (13.4)	0.128
Gender (% Male)	71.1	61.2	0.210	72	61.6	0.222
Race (% AA)	15.6	11.2	0.127	16.2	10.5	0.151
Retransplant (% Yes)	11.1	5.1	0.222	10.8	5.21	0.178
Causes of Liver Failure						
Hepatitis C	40	43.9	0.079	41.2	41.4	0.105
EtOH	22.2	22.4	0.005	17.6	29	0.271
NASH	13.3	20	0.186	5.47	5.22	0.011
HCC	22.2	19.4	0.067	8.54	8.79	0.009
Fulminant	2.22	6.12	0.196	2.94	4.35	0.075
MELD	21.5 (5.2)	20.1 (4.8)	0.284	19.9 (12.3)	20.2 (8.92)	0.169
Admit Severity of Illness						
Moderate	40	38.8	0.025	48.7	47.7	0.020
Major	31.1	48	0.360	29.7	43.3	0.293
Extreme	24.4	7.14	0.422	16.2	6.31	0.265
Pre-Transplant Labs						
Fibrinogen (ml/dL ± SD)	207.4 (87.7)	230.8 (92.7)	0.259	229.9 (104.6)	235.7 (114.5)	0.041
Creatinine (ml/dL ± SD)	1.19 (0.72)	1.10 (0.78)	0.119	.921 (0.058)	1.11 (0.737)	0.046
Total Bilirubin (ml/dL ± SD)	7.08 (9.46)	5.05 (6.27)	0.252	7.29 (6.88)	5.38 (6.40)	0.289
INR (ml/dL ± SD)	1.68 (0.35)	1.67 (0.47)	0.016	1.70 (1.06)	1.66 (0.82)	0.046

Propensity score analysis matching subjects receiving albumin only and HES only (1:2). The potential confounders (variables with univariate associations with AKI or HES use with $p < 0.20$) included severity of illness, MELD score, and NASH cirrhosis were included in the propensity score model. Severity of illness and MELD score were associated with HES use ($p = 0.021$ and $p = 0.111$) and NASH cirrhosis was associated with AKI ($p = 0.089$). HES = hydroxyethyl starch, EtOH = alcoholic, NASH = nonalcoholic steatohepatitis, HCC= hepatocellular carcinoma, MELD = model for end stage liver disease, INR= international ratio, SD = standard deviation