Perioperative colloid choice and bleeding in patients undergoing musculoskeletal surgery: An observational administrative database study

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Original Article

ABSTRACT

Background: The synthetic colloid hydroxyethyl starch (HES) received a black box warning, issued by the US Food and Drug Administration (FDA) in June 2013, in patients with sepsis, due to increased risk of bleeding, renal injury, and death. Risks of HES in populations undergoing noncardiac surgery are unclear. Here, we examine the association of colloid choice – human-derived albumin versus HES – with bleeding in musculoskeletal surgery.

Methods: Inpatient musculoskeletal surgical patients who received colloids on the day of surgery were included during a time period before the FDA warning on HES using the Premier Healthcare database. The exposure was type of colloids administered on the day of surgery: HES versus albumin. The primary outcome was major perioperative bleeding, measured on the 1st postoperative day through hospital discharge. The secondary outcomes included acute renal failure and postoperative length of stay >75th percentile.

Results: We identified 41,211 patients who received albumin (n = 12,803) and HES (n = 28,408) on the day of surgery. The propensity-weighted multivariable analysis demonstrated a reduced risk of major perioperative bleeding on the day after surgery following treatment with albumin versus HES (relative risk: 0.89 [95% confidence interval, 0.84–0.93]). No significant differences were observed in the secondary outcomes.

Conclusion: When compared with albumin, treatment with HES on the day of musculoskeletal surgery was associated with an increased risk of major perioperative bleeding on subsequent days. Given that HES continues to be used as a colloid in multiple patient populations worldwide, further studies examining the safety of HES versus albumin solutions are needed.

Key Words: Hemorrhage, hydroxyethyl starch derivatives, orthopedic procedures, surgical blood loss

INTRODUCTION

The use of colloids such as human-derived albumin and synthetic hydroxyethyl starch (HES) is common in the perioperative period. Given potential risks (mainly renal injury and bleeding), HES utilization has been controversial since the early 1970s. Meta-analyses examining the impact of colloid choice – albumin versus HES – in patients with sepsis and in patients undergoing cardiac surgery (with cardiopulmonary bypass) have...
found that red blood cell transfusions are increased when HES is used.\[5,6\]

The US Food and Drug Administration issued a boxed warning against the use of HES in critically ill adults in June 2013.\[7\] However, HES solutions are still used worldwide in various patient populations including but not limited to postpartum hemorrhage and combat casualties with hemorrhagic shock.\[4,8-10\] HES solutions are also used in patients undergoing musculoskeletal surgery, the most common major procedures.\[10,11\] The comparative safety of HES versus albumin in noncardiac surgery is unclear. Given the current concerns about HES, a large perioperative randomized trial comparing the safety of albumin versus HES in noncardiac surgery is unlikely.\[4,10,12\] Rigorous observational research is needed. Therefore, we sought to fill this gap in knowledge by examining the comparative perioperative safety of albumin versus HES in musculoskeletal surgery.

We hypothesized that in patients undergoing musculoskeletal surgery, HES would be associated with an increased risk of major perioperative bleeding, compared to albumin.\[5,6\]

**METHODS**

Our study was approved by the Duke University Health System’s Institutional Review Board. The requirement for written informed consent was waived by the Institutional Review Board (since we used de-identified administrative and financial data, Protocol #00046467). The manuscript adheres to the Strengthening the Reporting of Observational Studies in Epidemiology guidelines.

**Data source**

We formulated our study hypothesis before the extraction of data from the Premier Healthcare database (Premier Inc., Charlotte, NC, USA) between October 2008 and September 2014 (24 consecutive quarters). The database contains administrative information (clinical, demographic, and facility characteristics), International Classification of Diseases Ninth Revision Clinical Modification (ICD-9-CM) diagnosis and procedure codes, and detailed date-stamped billing data (for diagnostic tests, therapeutic procedures, and medications) from a large alliance of US hospitals.\[2,7,10\] A rigorous validation process is performed by Premier before data are incorporated into the database, including a seven-step integrity analysis and an iterative data validation and audit process.\[10,13,14\]

**Study cohort**

We identified adults admitted for inpatient surgery based on Medicare Severity Diagnosis-Related Groups codes. Using publicly available Agency for Healthcare Research and Quality clinical classification scheme software and ICD-9-CM procedure codes,\[15\] we restricted our cohort to patients undergoing surgery on the musculoskeletal system (primarily lower extremity joint arthroplasty). We further restricted the cohort to patients who had received colloids on the day of surgery (either HES or albumin) using date-stamped charge codes. The small proportion of patients who received both HES and albumin on the day of surgery was excluded. Thus, our final study cohort consisted of patients exposed to either albumin or HES on the day of surgery on the musculoskeletal system.

We examined the following demographic, clinical, and facility characteristics in our cohort: (1) age, gender, race, payer status, hospital size, teaching status, urban/rural location, and census region; (2) comorbidities defined by clusters of ICD-9-CM diagnosis codes; and (3) co-treatments defined by ICD-9-CM procedure codes or charge codes on the day of surgery. In addition to individual comorbidities, we computed the van Walraven score as a composite index of comorbidity.\[16\]

Co-treatments were identified based on specific day-stamped charge codes for treatments organized by organ system. These included the type of anesthesia (general, regional, and peripheral nerve blocks), mode of analgesia, use of neuromuscular blockers, use of steroids or insulin, and treatments related to the management of blood including (a) intravenous fluid treatments besides colloids (types and volumes of crystalloids); (b) vasopressor, inotrope, and diuretic use; (c) antifibrinolytics and anticoagulants; and (d) the use of other blood products.

**Analyses of outcomes**

Our primary outcome was major perioperative bleeding during the index hospitalization (measured on the 1st postoperative day through hospital discharge), defined as the receipt of red blood cell transfusion (using hospital charge codes and ICD-9 procedure code 99.1) or a hemorrhagic complication (ICD-9-CM code 998.11 or 998.12). The secondary outcomes included: (1) postoperative length of stay (>75th percentile), as a surrogate for significant in-hospital complications, and (2) postoperative acute renal failure as defined by ICD-9-CM codes (584.x, 586.x, 588.8, 588.9) or ICD-9 procedure code for dialysis catheter insertion or hemodialysis after surgery (38.95 or 39.95), in patients without renal failure on admission.

We used descriptive statistics to examine baseline differences in clinical, demographic, facility, and co-treatment characteristics of the study cohort and demonstrated differences using the standardized average mean difference.\[17,18\] To help control for confounding by indication, we estimated propensity scores as the probability of exposure (albumin versus HES). We
estimated both unadjusted and standardized mortality ratio-weighted relative risks of each clinical outcome, using a binomial regression model with a log-link function and robust standard errors, relaxing the assumption that observations from the same facility are independent.\cite{19,20} To test the robustness of the propensity score-weighted estimates, we conducted a sensitivity analysis using a multivariable binomial regression model without propensity weights. All analyses were performed using SAS Statistical Software version 9.4 (Cary, NC, USA).

**RESULTS**

Demographic and clinical characteristics

We identified 579,397 who underwent surgery in the musculoskeletal system between October 2008 and September 2014. Only 7.5% of the cohort (43,454) received colloid solutions on the day of surgery. After excluding dual colloid recipients (n = 2243), 41,211 (94.8%) were included in the analysis: 12,803 in the albumin group and 28,408 in the HES group.

Table 1 examines the demographics and clinical characteristics of the cohort. In the full cohort, the mean age for groups exposed to albumin and starch was 65 years (standardized mean difference [SMD] = 0.02) and 40% of the participants in both the groups were male. The propensity score-weighted mean van Walraven score in patients receiving albumin was 0.59, compared to 0.58 in patients who received HES (SMD = 0.003).

Table 1 examines the co-treatments in the cohort before propensity matching. The use of antifibrinolytic medications was higher in the HES group, while antithrombotic medication and parenteral nonsteroidal anti-inflammatory drug (NSAID) usage was higher in the albumin group. There was no difference between both the groups in the antiplatelet medication. More patients in the albumin group underwent neuraxial anesthetic techniques such as spinal and epidural anesthesia compared to the HES group. The primary vasopressor used was phenylephrine (43% in the albumin group versus 46% in the starch group).

Propensity matching

Clinical management of patients receiving albumin and HES was largely similar after propensity score weighting [Table 2]. After propensity matching, the higher incidence of patients in the albumin group receiving parenteral NSAIDs and neuraxial anesthetic techniques when compared to the HES group persisted. The higher incidence of the HES group receiving antifibrinolytic medications also persisted after propensity matching. There was no difference in the use of antithrombotic and

| Table 1: Demographic and clinical characteristics |
|-----------------------------------------------|
| Demographics                                  |
| Payor category managed care (%)               |
| Age (years)                                   |
| Male (%)                                      |
| Black (%)                                     |
| Comorbidities                                 |
| Van-Walraven score                            |
| Renal failure (%)                             |
| Deficiency anemia (%)                         |
| Liver disease (%)                             |
| Chronic blood loss anemia (%)                 |
| Coagulopathy (%)                              |
| Co-treatments                                 |
| Hematologic                                   |
| Antifibrinolytic medication (%)               |
| Antithrombotic medication (%)                 |
| Antiplatelet medication (%)                   |
| Anesthesia                                    |
| Anesthesia, regional, spinal/epidural (%)     |
| Anesthesia, general, intravenous (%)          |
| Anesthesia, general, inhaled (%)              |
| Anesthesia, regional, nerve block (%)         |
| Anesthesia, epidural (%)                      |
| Neuromuscular blocking agent (%)              |
| Benzodiazepine (%)                            |
| Cardiovascular*                               |
| Phenylephrine (%)                             |
| Renal                                         |
| Diuretic (%)                                  |
| Fluids                                        |
| Balanced crystalloid volume (liters)          |
| Saline volume (liters)                        |

\*Use of other vasopressors on the day of surgery was uncommon (<5% for all other vasopressors/inotropes). SMD: Standardized mean difference
antiplatelet medications between the two groups after propensity matching. After weighting, propensity score density curves showed good overlap, indicating reasonable comparability between the treatment groups [Table 2].

**Association between hydroxyethyl starch versus albumin on clinical outcomes**

Table 3 summarizes the association of albumin versus HES with the rate of major perioperative bleeding, as well as secondary outcomes, in the full sample. The primary analysis indicated that the rate of major bleeding was 16.8% in patients exposed to albumin, compared to 18.5% exposed to HES, with adjusted relative risks for major bleeding of 0.89 (95% confidence interval [CI], 0.84–0.93). The secondary outcomes were acute renal failure, adjusted relative risk: 0.89 (95% CI, 0.76–1.05), and a composite outcome of prolonged length of stay, adjusted relative risk: 1.01 (95% CI, 0.98–1.04). Results of sensitivity analyses revealed stable risk estimates.

**DISCUSSION**

Similar to previous studies looking at sepsis patients and cardiac surgery patients, we found a higher risk of major perioperative bleeding in patients exposed to HES on the day of surgery, compared to albumin. However, unlike previous studies, we did not see an increase in worsening renal dysfunction or length of hospital stay in patients exposed to HES, when compared to those who received albumin.

There are multiple takeaways from our study. First, albumin should be the preferred colloid in fluid resuscitation. Given the reduced risk of bleeding seen in patients exposed to albumin compared to HES, we can conclude that albumin may be associated with less bleeding when compared with starch solutions in patients undergoing common musculoskeletal surgeries. This is relevant to perioperative clinical practice in many parts of the world.

Second, we did not find an increased risk of acute renal failure with exposure to HES. The risk of acute renal failure in critically ill patients may be related to diminished physiologic reserve and compromised renal blood flow. In contrast, our study cohort was primarily composed of elective relatively healthy surgical patients, presumably without significant underlying physiologic derangement (van Walraven comorbidity index <1). Second, the use of starch solutions continues to be controversial. The proponents of HES continue to petition
the World Health Organization to ease restrictions,[12] while the opponents push for a total ban.[3,4] This is especially given the fact that HES continues to be used inappropriately even in populations where it is not supposed to be first line, as in the WOMAN trial.[8] Our study adds to the body of evidence that would support this point.

Our study has limitations. Over 95% of the patients exposed to HES received hetastarch solutions, not the newer tetrastarch solutions.[12] Whether albumin has an advantage over these low-molecular-weight HES solutions is unclear but beyond the scope of this study. Second, although we did examine transfusions based on both charge codes and ICD codes, we did not directly examine actual blood loss or nadir hemoglobin values as such clinical data are not available in the Premier database, give the administrative nature of the database and lack of granularity. Third, despite the rigorous use of restriction to control for measured confounders, our observational study remains at risk for residual unobserved confounding, specifically with regard to illness severity. Finally, the use of neuraxial anesthesia (spinal and epidural) was noted to be higher in the albumin. In orthopedic surgery, the use of neuraxial anesthesia either alone or in combination with general anesthesia has been associated with lower rates of blood transfusions when compared to general anesthesia alone.[21-23] This could contribute to the lower bleeding seen in the albumin group.

CONCLUSION

Compared to HES, exposure to albumin on the day of musculoskeletal surgery was associated with a decrease in risk of major perioperative bleeding on postoperative days. Given that HES continues to be used as a colloid in multiple patient populations worldwide, further studies examining the safety of HES solutions are needed.

Research quality and ethics statement

This study was approved by the Institutional Review Board / Ethics Committee at Duke University Health System (Approval # 00046467; Approval date Mar 1, 2020). Informed consent was waived by the IRB since only de-identified financial and administrative data were used. The authors followed the applicable EQUATOR Network (http://www.equator-network.org/) guidelines, specifically the STROBE Guidelines, during the conduct of this research project.

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Nil.

Conflicts of interest
There are no conflicts of interest.

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