Use of hydroxyethyl starch in leukocytapheresis procedures does not increase renal toxicity

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BACKGROUND: Hydroxyethyl starch (HES) is reportedly associated with an increased risk of renal failure and death when used for fluid resuscitation in critically ill patients. HES can be used during therapeutic leukocytapheresis (TL) procedures to enhance cell separation. The purpose of this study was to evaluate the occurrence of adverse events associated with HES during TL procedures.

STUDY DESIGN AND METHODS: We performed a retrospective review of patients who underwent TL with and without HES in the period 2009 to 2013 at six academic medical institutions.

RESULTS: A difference-in-difference regression analysis was used to estimate the mean change before and after TL in selected outcomes in the HES group relative to the average change in the non-HES group. Selected outcomes included serum creatinine, estimated glomerular filtration rate (eGFR), and white blood cell (WBC) count. A total of 195 patients who underwent 278 TL procedures were studied. We found no significant differences in serum creatinine levels and eGFR on Days 1 and 7 after TL procedure between patients who received and those who did not receive HES. The rate of adverse events and overall and early mortality were similar in both groups. Patients with acute myeloid leukemia who received HES had greater WBC reduction when HES was used. Additionally, patients who received HES had improvement in pulmonary leukostasis symptoms.

CONCLUSION: HES, used at low doses during TL procedures, was not associated with adverse events previously ascribed to its use as a volume expander.

Patients with acute leukemia presenting with hyperleukocytosis (white blood cell [WBC] count $> 50 \times 10^9$/L) are at risk for developing symptomatic leukostasis, disseminated intravascular

ABBREVIATIONS: AML = acute myeloid leukemia; CML = chronic myeloid leukemia; CMML = chronic myelomonocytic leukemia; DID = difference-in-difference; eGFR = estimated glomerular filtration rate; MS = molar substitution; RRT = renal replacement therapy; TL = therapeutic leukocytapheresis.

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coagulopathy, and tumor lysis syndrome. Hyperleukocytosis has been associated with poor prognosis and increased early mortality.[1] Therapeutic leukocytapheresis (TL) is a procedure intended to remove circulating leukemic cells. Although it is still controversial whether TL has impact on early mortality, TL can be considered as a coadjuvant therapeutic modality for patients presenting with rapidly increasing WBC count or with signs and symptoms suggestive of leukostasis.[2,3] Hydroxyethyl starch (HES) can be used during TL to enhance separation between WBCs and red blood cells during centrifugation resulting in more efficient WBC removal.

HES is derived from plant starches and consists of large starch molecules that can be added to saline to generate a colloidal solution. Owing to its volume-expanding properties, HES has been used for volume replacement in critically ill and surgical patients. Recent studies evaluating HES as volume replacement demonstrated that critically ill patients, especially those with sepsis, had an increased risk of renal failure compared to patients who did not receive HES.[4-17] These results prompted the US Food and Drug Administration to issue a "black box warning" about the dose-dependent risks associated with its use, including an increased risk of mortality and renal injury in critically ill patients and excess bleeding in patients undergoing open heart surgery associated with cardiopulmonary bypass.[18] These results and black box warning have resulted in the banning of the use of HES in some European countries and the limited use of HES in cases of hypovolemia not responding to crystalloid administration with a recommendation that HES should be used at the lowest effective dose for the shortest period of time.[19]

However, there are no definitive studies which have directly attributed use of HES with renal dysfunction or increased mortality during TL. The American Society for Apheresis (ASFA) commented on the risks of the use of HES and recommended avoiding the use of HES in critically ill patients, patients with renal insufficiency, patients with sepsis, and patients at risk of bleeding who are undergoing apheresis procedures and has recommended its use be limited to situations where the benefits of performing the indicated procedure outweigh the risks.[20] The aim of this study was to assess whether the use of HES during TL resulted in an increased rate of mortality, adverse events, and acute kidney injury compared to patients undergoing TL without HES.

MATERIALS AND METHODS

We performed a retrospective chart review of patients who underwent TL with and without HES in the period 2009 to 2013 at six academic institutions. The academic institutions were selected based on their experience with at least five TL procedures per year, and its geographical location representing different areas of the country (Northwest, Northeast, Midwest, and South). Institutional review board approval was obtained from all participating institutions. Only adult patients with myeloid or lymphoid malignancies were included. Data collected included age, sex, diagnosis, exposure to nephrotoxic medications within and after 7 days of the first and last TL procedure, chemotherapy treatment, indications for TL, procedure characteristics, and adverse events associated with the procedure. Serum creatinine levels, estimated glomerular filtration rate (eGFR), and the need for renal replacement therapy (RRT) were evaluated before and after each procedure and up to 7 days after the last TL procedure. Given the improvement in creatinine levels after the first TL in both groups, it was not possible to use the RIFLE (risk, injury, failure, loss of kidney function, and end-stage kidney disease) score to classify the renal injury. The severity of symptoms attributed to leukostasis was characterized using the Novotny score (Table 1), and patients were evaluated before and within 24 hours of each TL procedure.[21] The Novotny score attributes the probability of leukostasis syndrome based on severity of symptoms, 0 (leukostasis not present, no symptoms) to 3 (leukostasis highly probable, severe symptoms), and was calculated before and after each procedure.

The WBC count of the collection bag was not available to determine the efficiency of the collection, so the following formula [(preprocedure WBC count – postprocedure WBC count)/preprocedure WBC count] was used to assess cell depletion. At the two major institutions, samples were drawn immediately after the procedure was completed and the device was disconnected. The central line or peripheral IV (depending upon patient access) was flushed, and after an appropriate volume of blood was wasted, a sample for complete blood count was collected and sent for testing.

HES was used routinely at two institutions for all leukocytapheresis except when there was severely compromised renal function, history of reactions to HES, or history of allergy to corn (source of HES). The rationale for this use is based on the published literature demonstrating greater yields in granulocyte collections with the use of HES and extrapolating this to WBC reductions.[22] HES was not routinely used at the other four institutions. Only one of these institutions would consider using HES based on the cell type to be removed (i.e., myeloid malignancies) and apheresis attending physician's preferences. The mononuclear cell program (MNC) was the preferred mode across institutions used for procedures except when the peripheral smear demonstrated a more mature cell phenotype. The polymorphonuclear cell (PMN) program was utilized for chronic myelogenous or myelomonocytic leukemia or in the presence of an acute leukemia arising from existing chronic myelogenous leukemia. The preference for MNC is that in most acute leukemias, the size

TABLE 1. Probability of leukostasis based on severity of neurologic and respiratory symptoms: the Novotny score

Score	Probability of leukostasis	Severity of symptoms	Respiratory symptoms	Neurologic symptoms
0	Not present	No limitations	No limitations	No limitations
1	Possible	Slight limitations	Mild limitations, comfortable at rest	Mild tinnitus, headache, dizziness
2	Probable	Marked limitations	Comfortable only at rest	Slight visual disturbances, severe headache, tinnitus
3	Highly probably	Severe limitations	Dyspnea at rest, oxygen or respirator required	Severe visual disturbances, confusion, delirium, somnolence, intracranial hemorrhage

and density of the blasts will be in the range of a MNC and not a granulocyte.

Study data were collected and managed using REDCap (Research Electronic Data Capture) electronic data capture tools hosted at Children's National Medical Center. REDCap is a secure, Web-based application designed to support data capture for research studies, providing 1) an intuitive interface for validated data entry, 2) audit trails for tracking data manipulation and export procedures, 3) automated export procedures for seamless data downloads to common statistical packages, and 4) procedures for importing data from external sources.[23]

Statistical analysis

We used a quasi-experimental method known as difference-in-difference (DID).[24,25] The basic DID approach is as follows. First, the mean pre- versus post-difference in outcome in the HES group (Difference 1) and in the non-HES group (Difference 2) are calculated. Then, difference 2 is subtracted from difference 1. The result, DID = Difference 1 – Difference 2, is the pre- versus post-difference in outcome in the HES group net of the pre- versus post-difference in outcome in the non-HES group. For example, if the HES group showed a 10% decrease from Day 0 to Day 1 and the non-HES group showed a 15% decrease in the same period of time, the DID estimate would yield an actual net *in*crease in the HES group of 5% [–10% – (−15%)], compared to the non-HES group.

To improve the precision of the estimates, minimize bias, and obtain a reliable estimate of the statistical significance, we applied DID in a linear regression framework instead of calculating the differences arithmetically. We ran separate models for each outcome (dependent variable of the regression; serum creatinine, WBC count, eGFR, RRT, and symptomatic improvement [pulmonary and neurologic severity scores]). The serum creatinine, WBC count, and eGFR outcomes were log-transformed to mitigate the effect of outliers and also to estimate approximate percentage, rather than absolute, changes in outcome. Being dichotomous and ordinal variables, respectively, RTT and the clinical outcomes were used untransformed. The right-hand side of the DID equation includes only four variables: a subject-level indicator (also known as individual fixed effect), an indicator taking 1 if the observation is after treatment and 0 otherwise, and an indicator taking 1 if the observation is after treatment and comes from the HES group. This is a standard specification for a DID model.[24] The main coefficient of interest is associated to the latter variable, since it measures the change in outcomes for treatment observations during the posttreatment period. A positive and significant coefficient for observations that corresponds to both posttreatment and HES group can be interpreted as an outcome increase caused by the administration of HES. Conversely, a negative and significant coefficient can be interpreted as an outcome decrease caused by the administration of HES. The DID design removes all observed and unobserved time-invariant heterogeneity (demographics, number of procedures, days of admission, intensive care unit admission, diagnosis, etc.) across patients. The p values associated with t tests reported in the regression were based on heteroskedastic-robust standard errors.

Differences between the HES and non-HES groups for mortality (early and overall) and adverse events were analyzed using t tests. All statistical analyses were performed with computer software (STATA 8, StataCorp). A p value of less than 0.05 was considered significant for all statistical tests performed.

RESULTS

Patients and procedure characteristics

Descriptive analyses show that patients' characteristics were overall similar in both groups, with significant differences in race, FAB (French-American-British) leukemia classification, and disease severity (Table 2). Patients in the non-HES group had at baseline more severe neurologic and pulmonary leukostasis symptoms (Table 2).

TL procedure characteristics are described in Table 3. All procedures were done using an apheresis system (COBE Spectra, TerumoBCT). The mean number of procedures in the HES and non-HES groups were 1.3 and 1.4, respectively ($p = 0.368$). A total of 136 patients (69.7%) underwent one TL procedure, 46 (23.6%) patients underwent two procedures, 10 (5.3%) underwent three

TABLE 2. Patients' characteristics at baseline

Patient characteristics	All patients (n = 195)	HES (n = 70)	No HES (n = 125)	p value
Mean age (years)	56	56.3	55.9	0.886
Male sex*	122 (62.6)	44 (62.8)	78 (62.4)	0.95
Race*				
White	155 (78.9)	61 (87.1)	94 (74.2)	0.034
Black	19 (9.8)	8 (11.0)	11 (8.8)	0.567
Unknown or mixed	16 (8.2)	1 (1)	15 (12)	0.009
Native Hawaiian or other Pacific Islander	1 (1)	0	1 (1)	0.288
Asian	1 (1)	0	1 (1)	0.288
American Indian or Alaska Native	1 (1)	0	1 (1)	0.288
Diagnosis*				
AML	143 (73)	52 (74)	91 (73)	0.823
CML	18 (9)	7 (10)	11 (9)	0.783
CMML	5 (3)	3 (4)	2 (2)	0.257
Other†	29 (14)	8 (11)	21 (17)	0.314
AML FAB classification*		53	116	
M0	6 (3.5)	2 (4)	4 (3)	0.916
M1	11 (6.5)	7 (13)	4 (3)	0.017
M2	6 (3.5)	5 (9)	1 (0.8)	0.005
M3	3 (1.8)	0	3 (2)	0.24
M4	31 (18.3)	6 (11)	25 (21)	0.112
M5	42 (24.8)	20 (38)	22 (19)	0.009
M6	0	0	0	0
M7	1 (0.6)	0	1 (0.8)	0.501
Not applicable	69 (40.8)	13 (24)	56 (48)	0.003
Baseline, Day 0				
Hematocrit (%)	24.2	24.6	23.6	0.293
Platelets ($\times 10^9$/L)	82.95	86.7	79.2	0.674
WBCs ($\times 10^9$/L)	210	204.3	216.3	0.581
Blast (%)	61.5	59.3	63.7	0.39
Serum creatinine (mg/dL)	1.44	1.49	1.39	0.511
eGFR (mL/min/BSA)	53.8	50.4	57.2	0.103
Total days of admission	23.15	24.4	21.9	0.341
Severity score, neurologic (%) (n = 192)				
0		42	50	0.011
1		8	20	0.351
2		10	22	0.505
3		10	30	0.092
Severity score, respiratory (%) (n = 193)				
0		31	26	0.001
1		8	19	0.442
2		13	19	0.577
3		18	59	0.002

BSA = body surface area; FAB = French-American-British.
*Data are reported as number (%).
†Others include: 12 acute lymphoblastic leukemia (ALL); four pre-B-cell ALL; three T-cell ALL; two primary myelofibrosis; one chronic lymphocytic leukemia; one myeloid neoplasm with mixed myeloproliferative and myelodysplastic features with excess blasts (14% in marrow) and marked marrow fibrosis; one B-cell lymphoblastic leukemia; one lymphoid blast crisis of CML; one blast phase CML with mixed phenotype; one myeloproliferative neoplasm, unclassifiable; one CLL with flow and cytogenetics supporting mantle cell lymphoma.

TABLE 3. Characteristics of TL procedures

Apheresis procedures	HES (n = 91)	No HES (n = 187)
Mean number of procedures	1.3	1.4
Presence of symptomatic l eukostasis	69 (75.8)	166 (88.8)
Mode MNC	74 (81.3)	186 (99)
Mode PMN	17 (18.7)	1 (1)
Collection target		
2× blood volume	4 (4.3)	177 (94.6)
3 hr	57 (62.6)	1 (0.5)
Cell count $< 50 \times 10^9$/L	21 (23)	0
10 L	9 (9.9)	9 (4.8)
Mean HES dose	9.08 mL/kg	NA

procedures, and three patients (1.4%) required four procedures. The HES formulation used across institutions was hetastarch (6% in 0.9% sodium chloride, 600/0.7; Hespan, DuPont Critical Care, Inc.).

Outcomes

Outcome trends show that renal function, as measured by serum creatinine levels and eGFR, and WBC counts improved throughout the 7-day period after first TL procedure in both groups (Fig. 1). Descriptive analyses indicate that renal function, need for RRT, WBC count, mortality, and adverse events were similar in both groups on Days 0,

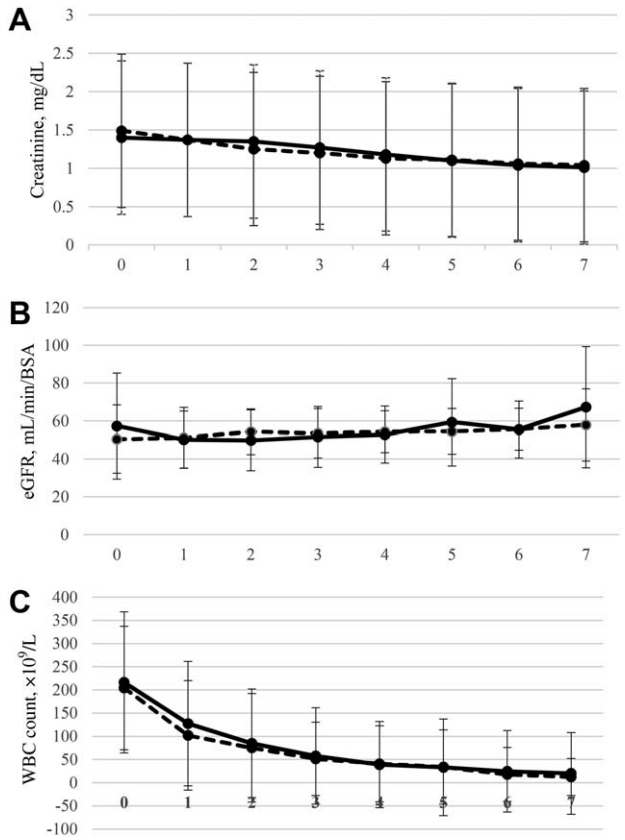

Fig. 1. Outcome trends from Day 0 (before TL) through Day 7. (A) Mean serum creatinine levels, (B) mean eGFR, and (C) mean WBC count before and 7 days after the first TL procedure. Mean serum creatinine levels and WBC count decreased and eGFR increased in both groups throughout the first 7 days. (– – –) HES; (—) no HES.

1, and 7 (Table 4). The rate of adverse events was similar in both groups, with a total of four TL-related adverse events in the HES group (two mild citrate toxicity, one probable volume overload, and one patient with a history of seizure disorder, who developed seizures incidental to the TL procedure) and eight events in the non-HES group (four citrate toxicity, one venous access related, one low-level bleeding from the line, one vasovagal reaction; Table 4).

The DID regression analyses showed that percent changes in serum creatinine levels and eGFR between the two groups were not significant (Table 5). However, WBC reduction was significantly greater on Day 1 in the HES group when compared to the non-HES group (DID = −26.4%; p = 0.002). On Day 7, there were no differences in WBC count between the two groups (Table 5). The DID regression analysis also showed that the percent change in the pulmonary severity score was significantly more favorable after TL for patients who received HES compared to patients who did not receive HES

TABLE 4. Descriptive statistics, outcome variables*

Outcomes	HES (n = 70)	No HES (n = 125)	p value
Serum creatinine (mg/dL)			
Day 0	1.49	1.39	0.511
Day 1	1.37	1.36	0.972
Day 7	1.04	1.01	0.805
eGFR (mL/min/BSA)			
Day 0	50.4	57.2	0.103
Day 1	51.15	50.2	0.744
Day 7	57.91	67.26	0.071
RRT†			
Before first procedure	3 (4.3)	1 (0.8)	0.101
After first procedure	7 (10)	7 (5.6)	0.256
WBCs (×10⁹/L)			
Day 0	204	216	0.581
Day 1	102.01	127.5	0.188
Day 7	12.8	20.27	0.546
Overall mortality†	12 (18)	32 (26)	0.266
Early mortality†	7 (10)	22 (18)	0.115
Adverse events†	4 (5.7)	8 (6.4)	0.849

*Mean serum creatinine levels, eGFR, WBC, need for RRT, and mortality (early and overall) were not significantly different when HES and no-HES groups were compared at three different time points (Days 0, 1, and 7).
†Data are reported as number (%).

TABLE 5. DID regression estimates for selected outcomes

Variable	Change (p value)
Serum creatinine, % change	
Day 0 to Day 1	−1.1% (p = 0.696)
Day 0 to Day 7	8.8% (p = 0.262)
eGFR, % change	
Day 0 to Day 1	4.7% (p = 0.108)
Day 0 to Day 7	−4.8% (p = 0.519)
WBC, % change	
Day 0 to Day 1	−26.4% (p = 0.002)
Day 0 to Day 7	−20.5% (p = 0.511)
Severity score, before and after % change	
Pulmonary	−0.25 (p = 0.013)
Neurologic	−0.050 (p = 0.727)

(DID = −0.25; p = 0.013; Fig. 2; Table 5). The advantage for the HES group was not seen with neurologic symptoms (DID = −0.050; p = 0.727).

When separate models for acute myeloid leukemia (AML) and chronic myelomonocytic leukemia (CMML) or chronic myeloid leukemia (CML) were run, the WBC reduction was significantly greater on Day 1 in the HES group when compared to the non-HES group (DID = −26.3%; p = 0.006) for AML, and higher, but not significant, for CMML or CML (DID = −27.5%; p = 0.170).

The fraction of cells removed [(preprocedure WBC count – postprocedure WBC count)/preprocedure WBC count] was statistically larger in patients with diagnosis of AML when using HES (59 ± 20%), compared to a similar

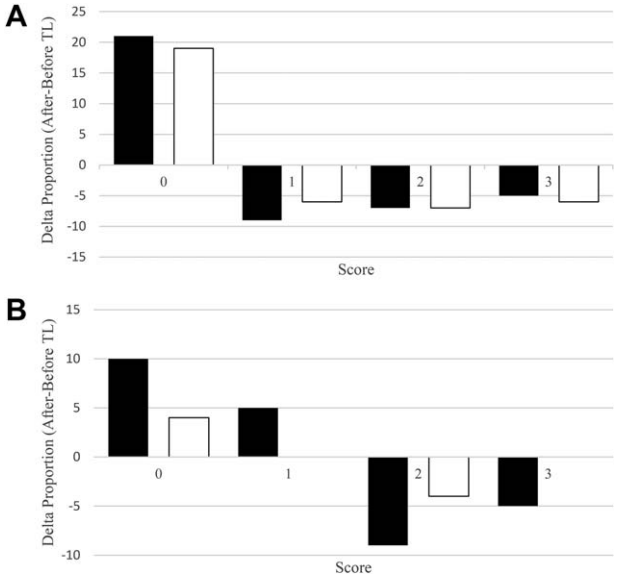

Fig. 2. Change in leukostasis symptoms classified using the Novotny scores before and after TL procedures. (A) Neurologic symptoms: there is a positive delta (increment) proportion of patients with score 0 (less symptoms) after TL and a negative delta (decrease) for severity scores 1, 2, and 3 (interpreted as improvement), in HES and no-HES groups. (B) Respiratory symptoms: there is a positive delta (increment) proportion of patients with severity score 0 (fewer symptoms) in both groups and with severity score 1 only for HES group. There is a negative delta (decrease) proportion of patients with severity score 2 in both groups and with severity score 3 for the HES group. There is null delta (no change) proportion of patients with severity score 3 in the no-HES group. (■) HES; (□) no HES.

cohort of patients not using HES (47 ± 19%, p = 0.001). For patients with the diagnosis of CML or CMML, the fraction of cells removed when using HES and not using HES was 41 ± 33 and 28 ± 25%, respectively (p = 0.345). Patients with lymphoid malignancies had similar fraction of cells removed when using HES and no HES, 60 ± 23 and 46 ± 23%, respectively (p = 0.175).

DISCUSSION

Studies using HES as a volume expander in critically ill patients admitted to the intensive care unit, as well as surgical patients, have concluded that HES is associated with increased renal failure and mortality, particularly in septic patients.[6] We found no increase in renal toxicity, mortality, or adverse events in 70 patients undergoing TL using HES compared to 125 patients who underwent TL without HES. The lack of nephrotoxicity in our group of patients is not likely related to differences in HES formulation or patients' underlying medical condition.

Starch formulations have significant differences in metabolism and elimination, mainly determined by the molar substitution (MS). The MS represents the amount of hydroxyethyl residues attached to the anhydrous glucose particles, and the level of substitution determines the solubility of the starch in water and degradation rate. HES formulations are named based on the MS as hetastarch (MS = 0.7), hexastarch (MS = 0.6), pentastarch (MS = 0.5), and tetrastarch (MS = 0.4), and the lower the substitution the higher the degradation and smaller the retention in circulation. In other words, the more highly substituted HES formulation (i.e., hetastarch), the greater the accumulation compared to a less substituted HES (i.e., tetrastarch). HES concentration, molecular weight, MS, and pattern of substitution determine the accumulation rate and the maximum daily dose.[26] The maximum recommended daily dose of 6% HES is 1500 mL or not to exceed 20 mL/kg.[26,27]

Most studies evaluating renal function and mortality in septic and critically ill patients receiving HES used tetrastarches, which have a better elimination profile compared to hetastarch. Whether these different formulations affect renal outcomes is uncertain.[6] However, we did not observe adverse events associated to HES accumulation. In studies in which nephrotoxicity was observed, the HES dose ranged from 1.7 L in 24 hours to 70 mL/kg with median duration of 14 days.[7,28] Our patient population received a much smaller dose with a mean of 9.08 mL/kg, which is within the limits of the maximum recommended dose. In addition, HES was only used in the context of the TL procedure and not for volume expansion.

A recent meta-analysis concluded that septic patients are at higher risk of renal injury when compared to surgical patients, and the use of HES could contribute to the increased risk of renal failure by unknown mechanisms. It was speculated that changes in the plasma viscosity or reticuloendothelial system function could contribute to this increase in toxicity.[6] Patients with hematologic malignancies are at increased risk of renal failure as evidenced by the increased creatinine in our cohort of patients and previous reports.[29,30] Our findings suggest that the use of HES did not worsen the renal outcomes. Furthermore, the renal function improved in the HES and non-HES groups. It is important to mention that patients with renal dysfunction were not excluded from the use of HES during the procedure

The use of HES has been reported to improve WBC collection yield.[31] We observed a significant WBC reduction in patients receiving HES. When we separately evaluated AML and CML or CMML patients, patients with AML had greater WBC reduction when HES was used. An important possible bias to mention is that the majority of patients receiving HES came from two institutions and

differences in chemotherapy regimens could also contribute to WBC count after TL treatment. Timing of the sample collection to determine the WBC count may differ across institutions as well. The lack of significance in the CML or CMML groups' WBC removal could be partially explained by the relatively small sample size (n = 23). An alternative explanation is that CML and CMML represent chronic leukemia with significant tumor involvement of the spleen. It is possible that mobilization of WBCs from the patients' enlarged spleens resulted in a failure to reduce the patients' circulating WBC mass. Furthermore, the formula we used to calculate the efficiency does not account for the WBC count in the bag, and as a result, the removal of cells is underestimated when rapid mobilization occurs from the spleen. We also observed that patients who received HES had a significant improvement of pulmonary symptoms when compared to patients who did not receive HES. The short- and long-term mortality was similar in both groups, so the clinical implications of this symptomatic improvement are uncertain.

HES is also commonly used during granulocyte collections from healthy donors, who typically receive steroids and/or granulocyte–colony-stimulating factor to increase granulocyte yields. Approximately 450 to 475 mL of HES is used per procedure. Renal function is not routinely evaluated in these patients. Adverse events associated with the use of HES during these donations are limited to pruritus (up to 6% in one series) and very rare allergic reactions (<0.1% of collections).[32]

For therapeutic plasma exchange procedures, HES, alone or in combinations with albumin replacement, has been used for patients who do not wish to receive blood products with an acceptable safety profile.[33-36] Chronic HES exposure (130 L within 20 months) can lead to an acquired lysosomal storage disease with symptomatic, massive, diffuse tissue infiltration of HES-laden foamy macrophages.[37,38] Kidney failure after chronic TPE using low-dose (60 g) HES combined with albumin as replacement fluid has also been described.[39]

HES has been associated with adverse events including allergic reactions that ranged in severity from mild to anaphylactic reactions. A study that evaluated colloid plasma substitutes at 31 hospitals in Germany, including 16,405 HES infusions, described a calculated incidence of severe anaphylactoid reactions (shock or cardiac or respiratory distress) of 0.006%.[40] We did not observe allergic reactions in our cohort of patients.

Dose-dependent coagulation abnormalities and risk of bleeding were also described in patients receiving HES.[41] Low doses of HES are associated with minor abnormalities of coagulation test results that are usually not clinically significant.[42] Massive amounts of HES, more than 25% blood volume, have been studied in dogs and were associated with bleeding partially attributed to dilution effect.

This study has several weaknesses, including its retrospective nature, inability to calculate collection efficiency of the TL procedures, possible differences in chemotherapy regimens, and site bias. Although there were six institutions included in this study, only two of these institutions accounted for 82% of TL procedures where HES was used. These weaknesses prevent drawing definite conclusions, but the results of this study suggest that HES, when used in low doses, does not result in renal injury, improves pulmonary status of patients undergoing TL, and can improve leukoreduction efficiency.

In summary, although there is extensive evidence that fluid resuscitation using HES can result in renal impairment and increase mortality, these adverse effects were not seen in adult patients undergoing TL with HES. Further studies are required to confirm the finding of improvement of pulmonary leukostasis syndrome using HES during TL.

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CONFLICT OF INTEREST

The authors have disclosed no conflicts of interest.

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