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

Monica B Pagano[1], Charles Harmon[2], Laura Cooling[2], Laura Connelly-Smith[3], Steven A. Mann[4], Huy P. Pham[5], Marisa B. Marques[5], Annette J Schlueter[6], Rosemary Case[7], Karen E King[7], Guido Cataife[8], Yanyun Wu[9], Edward CC Wong[10], Jeffrey L Winters[11]

1. University of Washington, Department of Laboratory Medicine, Seattle WA.
2. University of Michigan, Department of Pathology, Ann Arbor, MI
3. University of Washington, Division of Hematology, Seattle WA.
4. University of Alabama School of Medicine, Birmingham AL
5. University of Alabama at Birmingham, Department of Pathology, Birmingham AL
6. University of Iowa, Department of Pathology, Iowa City IA
7. Johns Hopkins Medical Institutions, Division of Transfusion Medicine Baltimore, MD.
8. IMPAQ International, Health Division, Columbia MD.
9. Bloodworks Northwest, Seattle WA.
10. Children's National Medical Center, Division of Laboratory Medicine, George Washington School of Medicine and Health Sciences, Departments of Pediatrics and Pathology
11. Mayo Clinic, Department of Laboratory Medicine and Pathology, Division of Transfusion Medicine, Rochester MN.

Corresponding author:

Monica B Pagano, MD

University of Washington

1959 NE Pacific St

Seattle, WA 98195

Telephone: 425-387-0491

Fax: 206-598-6189

monibea@uw.edu

Running head: HES and therapeutic leukocytapheresis

Conflict of interest disclosures: The authors declare no competing financial interests.

Word count: Abstract: 242 Manuscript: 2835 Figures 2 Tables 5 Reference count: 40

Abstract

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 – 2013 at six academic medical institutions. Results: A difference-in-difference (DID) regression analysis was used to estimate the average 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 count (WBC). One hundred and ninety five patients who underwent 278 TL procedures were studied. We found no statistically significant differences in serum creatinine levels and eGFR at day 1 and day 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 AML 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.

Introduction

Patients with acute leukemia presenting with hyperleukocytosis (white blood cell count > 50,000 – 100,000/mL) are at risk for developing symptomatic leukostasis, disseminated intravascular 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 rising white blood cell count (WBC) or with signs and symptoms suggestive of leukostasis. [2,3] Hydroxyethyl starch (HES) can be used during TL to enhance separation between leukocytes and red cells during centrifugation resulting in more efficient white cell removal.

HES is derived from plant starches and consists of large starch molecules that can be added to saline to generate a colloidal solution. Due 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 FDA 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 as compared to patients undergoing TL without HES.

Methods

We performed a retrospective chart review of patients who underwent TL with and without HES in the period 2009 – 2013 at six academic institutions. The academic institutions were selected based on their experience with at least 5 TL procedures per year, and its geographical location representing different areas of the country (Northwest, Northeast, Midwest, and South). IRB approval was obtained from all participating institutions. Only adult patients with myeloid or lymphoid malignancies were included. Data collected included age, gender, 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 seven 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 [(WBC Pre procedure – WBC Post procedure)/WBC Pre procedure] 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 wasting an appropriate volume of blood, a sample for CBC 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 upon the published literature demonstrating greater yields in granulocyte collections with the use of HES and extrapolating this to leukocyte reductions. [22] HES was not routinely used at the other four institutions. Only one of these institutions would consider to use 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 program (PMN) was utilized for chronic myelogenous/myelomonocytic leukemia, or in the presence of an acute leukemia arising from a pre-existing chronic myelogenous leukemia. The preference for MNC is that in most acute leukemias, the size/density of the blasts will be in the range of a mononuclear cell 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 vs. post difference in outcome in the HES group (labeled *difference 1*) and in the non-HES group (labeled *difference 2*) are calculated. Then, difference 2 is subtracted from difference 1. The result, DID = difference 1– difference 2, is the pre vs. post difference in outcome in the HES group net of the pre vs. 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, eGFR, RRT, and symptomatic improvement (pulmonary and neurologic severity scores)]. The serum creatinine, WBC, 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 post-treatment and 0 otherwise, and an indicator taking 1 if the observation is post-treatment and comes from the HES group. This is a standard specification for a DID model. [24] The main coefficient of interest is the associated to the latter variable, since it measures the change in outcomes for treatment observations during the post-treatment period. A positive and statistically significant coefficient for observations that corresponds to both post-treatment and HES group can be interpreted as an outcome increase caused by the administration of HES. Conversely, a negative and statistically 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, ICU 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 in STATA 8 (StataCorp, College Station, TX). A p value <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 COBE Spectra (TerumoBCT, Lakewood, CO). The average number of procedures in the HES and non-HES group were 1.3 and 1.4 respectively (p=0.368). One hundred thirty six patients (69.7%) underwent one TL procedure, 46 (23.6%) patients underwent 2 procedures, 10 (5.3%) underwent 3 procedures, and 3 patients (1.4%) required 4 procedures. The HES formulation used across institutions was hetastarch (6% in 0.9% sodium chloride, 600/0.7) (Hespan, DuPont Cirtical Care, Inc, Waukegan, IL)

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 (Figure 1).

Descriptive analyses indicate that renal function, need for RRT, WBC count, mortality and adverse events were similar in both groups on days 0, 1, and 7 (Table 4). The rate of adverse events was similar in both groups, with a total of 4 TL related adverse events in the HES group (2 mild citrate toxicity, 1 probable volume overload, and 1 patient with a history of seizure disorder, who developed seizures incidental to the TL procedure) and 8 events in the non-HES group (4 citrate toxicity, 1 venous access related, 1 low level bleeding from the line, 1 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, white blood cell 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 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 received HES (DID=-0.25; p=0.013) (Figure 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 AML and CMML/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 statistically significant, for CMML/CML (DID=-27.5% p=0.170).

The fraction of cells removed [(WBC Pre procedure – WBC Post procedure)/WBC Pre procedure] was statistically larger in patients with diagnosis of AML when using HES (59% +/- 20%), compared to a similar cohort of patients not using HES (47% +/- 19%, p= 0.001). For patients with the diagnosis of CML/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 ICU, 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 as 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. The molar substitution 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 molar substitution (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, molar substitution, and pattern of substitution, determine the accumulation rate and the maximum daily dose. [26] The maximum recommended daily dose of 6% HES is 1,500 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 an average 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 hematological 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/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 2 institutions and differences in chemotherapy regimens could also contribute to WBC after TL treatment. Timing of the sample collection to determine the WBC count may differ across institutions as well. The lack of statistical significance in the CML/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 (GCSF) to increase granulocyte yields.

Approximately 450-475 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 not 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, cardiac or respiratory distress) of 0.006%. [40] We did not observed 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, > 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 6 institutions included in this study, only 2 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 leukodepletion 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.

Acknowledgements: This publication was supported by Award Number UL1TR000075 from the NIH National Center for Advancing Translational Sciences. Its contents are solely the responsibility of the authors and do not necessarily represent the official views of the National Center for Advancing Translational Sciences or the National Institutes of Health. The authors would like to thank the ASFA research subcommittee members for helpful discussions on the design of this project and results.

Authorship contributions: Conception and design MBP, LC, JLW, YW. Data Collection CH, LC, JLW, LCS, SAM, HPP, MBM, AJS, RC, KEK. Data analysis and interpretation GC, MBP, LC, JLW. Manuscript writing MBP, LC, LCS, MBM, AJS, KEK, GC, YW, ECCW, JLW.

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

Table 2. Patients' characteristics at baseline

Patient characteristics	All patients, N=195	HES, N=70	No HES, N=125	P
Age, years (mean)	56	56.3	55.9	0.886
Male sex, n (%)	122 (62.6)	44 (62.8)	78 (62.4)	0.95
Race, n (%)				
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, n (%)				
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, n (%)		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
Non applicable	69 (40.8)	13 (24)	56 (48)	0.003
Baseline, day 0				
Hematocrit, %	24.2	24.6	23.6	0.293
Platelet, thousand/μL	82.95	86.7	79.2	0.674
WBC, thousand/μL	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

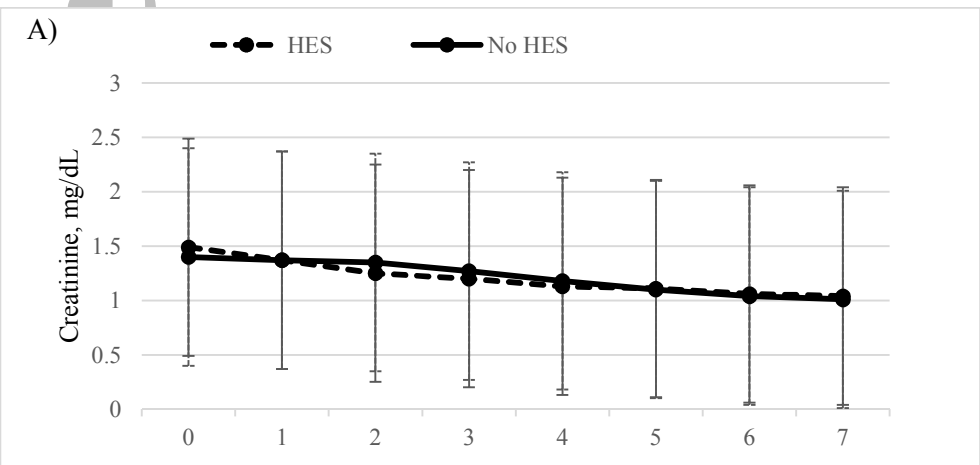
Note: AML: acute myeloid leukemia, CML: chronic myeloid leukemia, CMML: chronic myelomonocytic leukemia, FAB: French-American-British, eGFR: estimated glomerular filtration rate, BSA: body surface area.

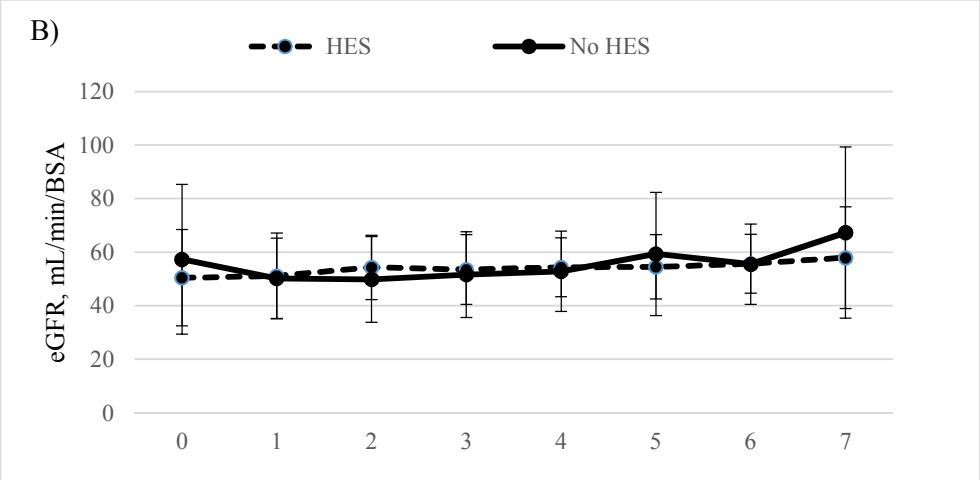
Others include: 12 acute lymphoblastic leukemia (ALL), 4 pre-B cell ALL, 3 T cell ALL, 2 primary myelofibrosis, 1 chronic lymphocytic leukemia, 1 myeloid neoplasm with mixed myeloproliferative and myelodysplastic features with excess blasts (14% in marrow) and marked bone marrow fibrosis, 1 B cell lymphoblastic leukemia, 1 lymphoid blast crisis of CML, 1 blast phase CML with mixed phenotype, 1 myeloproliferative neoplasm, unclassifiable, 1 CLL with flow and cytogenetics supporting mantle cell lymphoma.

Table 3. Characteristics of therapeutic leukocytapheresis procedures

Apheresis procedures	**HES, N = 91**	**No HES, N = 187**
Average number of procedures	1.3	1.4
Presence of symptomatic leukostasis	69 (75.8)	166 (88.8)
Mode MNC	74 (81.3)	186 (99)
Mode PMN	17 (18.7)	1 (1)
Collection target		
2 x Blood volume	4 (4.3)	177 (94.6)
3 Hours	57 (62.6)	1 (0.5)
Cell count < 50 K	21 (23)	0
10 liters	9 (9.9)	9 (4.8)
Average HES dose per Kg	9.08 mL/Kg	NA

Figure 1. **Outcome trends from day 0 [before therapeutic leukocytapheresis (TL)] through day 7**. A) Mean serum creatinine levels, B) mean estimated glomerular filtration rate (eGFR), and C) mean white blood cell count (WBC) before and 7 days after the first TL procedure. Mean serum creatinine levels and WBC decreased and eGFR increased in both groups throughout the first 7days.





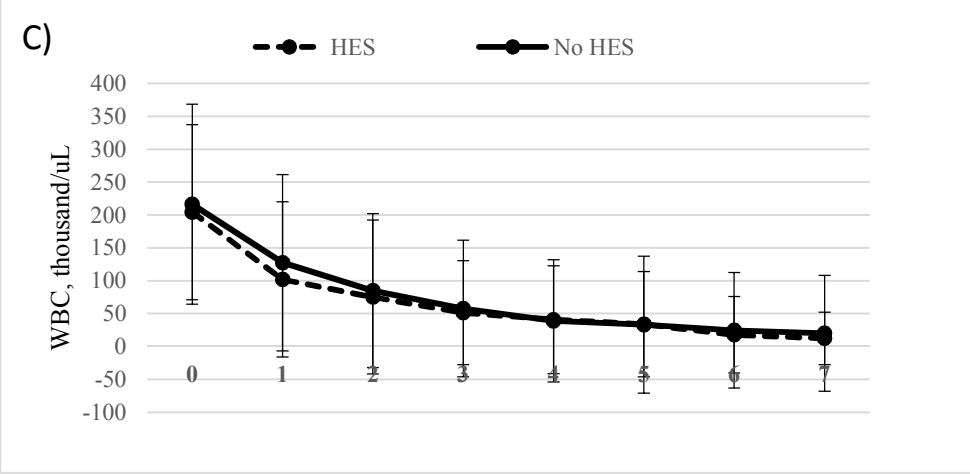
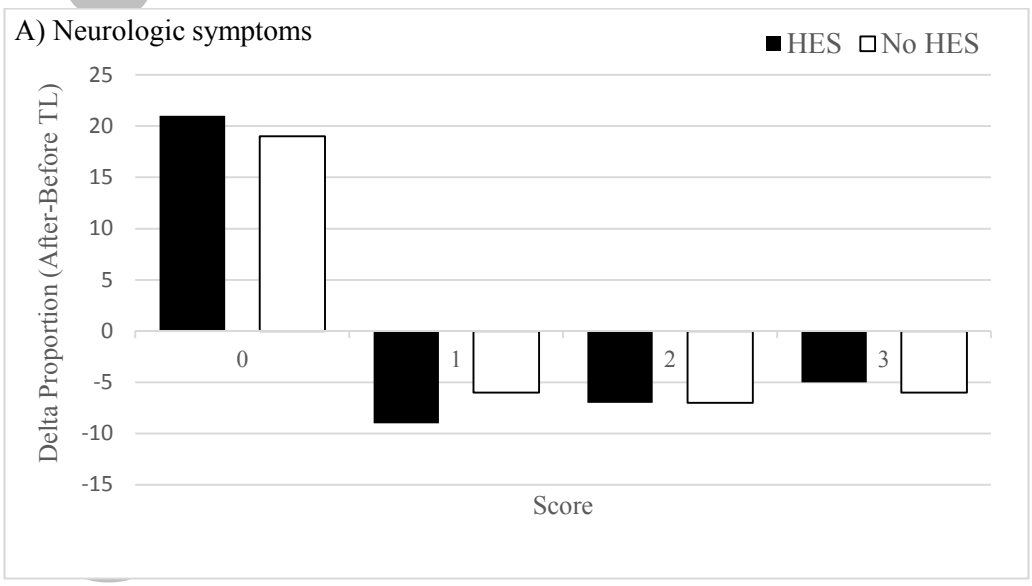


Table 4. **Descriptive statistics, outcome variables.** Mean serum creatinine levels, eGFR, WBC, need for RRT and mortality (early and overall) were not significantly different when compare HES and No HES groups at three different time points (day 0, day 1 day 7).

Outcomes	HES, N=70	No HES, N=125	P
Serum creatinine mg/dL, day 0	1.49	1.39	0.511
Serum creatinine mg/dL, day 1	1.37	1.36	0.972
Serum creatinine mg/dL, day 7	1.04	1.01	0.805
eGFR mL/min/BSA, day 0	50.4	57.2	0.103
eGFR mL/min/BSA, day 1	51.15	50.2	0.744
eGFR mL/min/BSA, day 7	57.91	67.26	0.071
RRT before first procedure, n (%)	3 (4.3)	1 (0.8)	0.101
RRT after first procedure, n (%)	7 (10)	7 (5.6)	0.256
WBC thousand/μL, day 0	204	216	0.581
WBC thousand/μL, day 1	102.01	127.5	0.188
WBC thousand/μL, day 7	12.8	20.27	0.546
Overall mortality, n (%)	12 (18)	32 (26)	0.266
Early mortality, n (%)	7 (10)	22 (18)	0.115
Adverse events, n (%)	4 (5.7)	8 (6.4)	0.849

Note: eGFR: estimated glomerular filtration rate; RRT renal replacement therapy; WBC: white blood cell count

Figure 2. **Change in leukostasis symptoms classified using the Novotny scores before and after leukocytapheresis (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 (less 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.



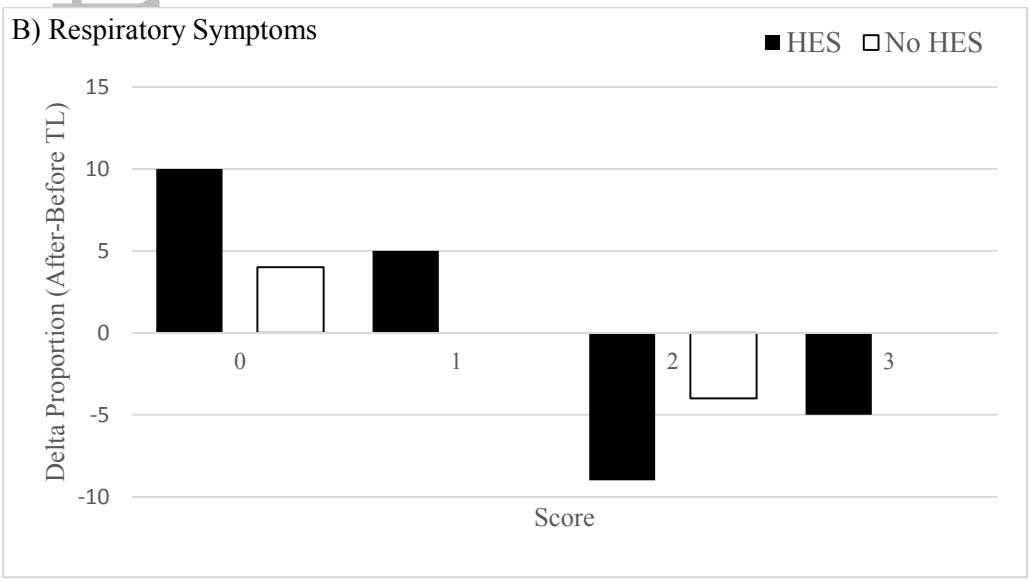


Table 5. Difference in difference (DID) regression estimates for selected outcomes

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

Note: eGFR: Estimated glomerular filtration rate, WBC: White blood cell

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