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A study on beneficial impact of the use of medium-molecular-weight hydroxyethyl starch in granulocyte apheresis using continuous-flow cell separator Spectra Optia: A retrospective single-center study at a tertiary care oncology center

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Abstract:

INTRODUCTION: Granulocyte transfusion is one of the best therapeutic modalities in prolonged neutropenic patients with severe bacterial/fungal infections. Granulocyte harvest using conventional acid citrate dextrose (ACD) anticoagulant (ACD-A) by apheresis is not satisfactory in comparison to the use of hydroxyethyl starch (HES), but the latter is associated with various adverse events, especially with high-molecular-weight HES.

AIMS AND OBJECTIVE: This study aimed to assess the beneficial impact of the use of medium-molecular-weight (MMW)-HES and trisodium citrate combination over ACD-A in granulocyte apheresis when using Spectra Optia.

MATERIALS AND METHODS: This was a retrospective study comparing granulocyte harvest results with the use of ACD or HES and trisodium citrate combination. All the donors in both the groups received single 600 μg of granulocyte colony-stimulating factor subcutaneous injection followed by 8 mg of dexamethasone tablet 10–12 h and omnacortil 60 mg orally 3 h before harvest. A number of adverse incidents, if any, were observed and noted. Donor/procedure parameters were compared using Mann–Whitney *U*-test/unpaired *t*-test.

RESULTS: Granulocyte yield (mean: 3.29×10^{10}/unit vs. 4.5×10^{10}/unit in the ACD and HES groups, respectively, $P \leq 0.0001$) was significantly better in the HES group. The collection efficiency was also better in the HES group (mean: 15.86% vs. 26.70% in the ACD and HES groups, respectively, $P \leq 0.0001$) in the ACD and HES groups, respectively. There was no significant adverse event noted in any of these two groups.

CONCLUSION: In our study, granulocytes with optimum yield can be easily harvested with Spectra Optia cell separator using 6% HES (MMW) and trisodium citrate combination with standard 12-h interval gap between mobilization and harvest. This strategy can also have no or minimal extra cost burden to patients.

Keywords:

Acid citrate dextrose, adverse events, granulocyte apheresis, hydroxyethyl starch, leukapheresis

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Introduction

Severe neutropenia and bacterial or fungal infections, either chemotherapy-induced or postallogeneic stem cell transplantation, lead to morbidity and mortality. Direct correlation is there between the risk of infections and the duration and degree of neutropenia. Neutrophil counts and marrow production are essential for achieving recovery from infections, as they are the strongest predictors of recovery. Therefore, granulocyte transfusion (GTX) therapy is filling the gap between bone marrow suppression and neutrophil recovery.

For patients with severe neutropenic sepsis not responding to first-line antibiotics or antifungal medication, GTX therapy can be an effective alternative to restore normal polymorphonuclear neutrophil counts in the bloodstream. The use of granulocyte concentrates in these patients has been studied since the 1930s for their effectiveness. During the 1970s, the following factors aid to achieve good yield from healthy blood donors – the introduction of continuous-flow apheresis technique for leukapheresis, the use of hydroxyethyl starch (HES) as a sedimenting agent, and the use of steroids as a stimulating agent.[1-4]

In the 1990s, the use of recombinant human granulocyte colony-stimulating factor (rhG-CSF) as a single subcutaneous dose has augmented neutrophil counts by up to fivefold. Later on, the combined use of rhG-CSF and steroids has found out more beneficial and effective. The synergistic effect of these two agents resulted in even higher granulocyte yield harvested by apheresis.[5-9] However, a voluntary blood donor for granulocyte harvest is challenging and often not available.

In this study, we evaluate the beneficial impact of 6% HES (medium molecular weight [MMW]) and 46.7% trisodium citrate over acid citrate dextrose (ACD) for granulocyte apheresis with the use of Spectra Optia cell separator.

Materials and Methods

Study design and period

The current study is a retrospective one in which granulocyte apheresis procedures took place between December 2015 and September 2021 in the department of transfusion medicine.

Study group

The study included two groups: one consisting of donors who received MMW (130 kDa/0.4) HES and 46.7% trisodium citrate combination during granulocyte harvest named as HES group and another, who received only ACD-A named as ACD group.

Stratification criteria

The period of the ACD group included donors from December 2015 to January 2019, whereas the HES group spanned from February 2019 to September 2021.

Inclusion criteria

All donors were screened as per blood donation criteria by the Drugs and Cosmetics Act and Rules, 1945. Only those donors who had been harvested using the Spectra Optia apheresis system during this period were included in the study.

Exclusion criteria

Donors not fulfilling normal blood donation criteria as per the Drugs and Cosmetics Act and Rules 1945 or those whose harvest was done using other machines were excluded from the study.

Donor mobilization protocol

Both the groups followed the same mobilization protocol by the department of hematology and bone marrow transplant (BMT) as described by Higby *et al*.[10] All the donors in both the groups received single 600 µg of G-CSF subcutaneous injection followed by 8 mg of dexamethasone tablet 10–12 h and omnacortil 60 mg orally 3 h before harvest.

Methodology

- Voluntary blood donation form and informed consent were obtained for the procedure after donors were properly explained by the transfusion medicine physician in the department of transfusion medicine
- Donor screening was done as per normal blood donation criteria laid by the Drugs and Cosmetics Act amendment made on March 2020
- Selected donors were checked for proper venous access in both antecubital veins. Blood samples for complete blood count and other testing were obtained
- The minimal platelet count needed for this procedure was kept at 150,000/µL and the total leukocyte count (TLC) was 4000–11,000/µL and Hb was fixed to be 12.5–17.5 g/dl
- Blood group typing, antibody screening, and major crossmatch were performed between the donor and the recipient
- Donor blood was also screened for the presence of transfusion-transmissible diseases such as HIV, hepatitis B and C, malaria, and syphilis
- Suitable donors were subsequently taken for mobilization protocol
- Following the procedure, the yield of both the procedure and extraction coefficient of the machine was calculated using the following formula.

Collection efficiency (CE) was calculated using the equation as follows:

CE (%) = (Granulocyte cell yield/[preapheresis number of granulocyte cells in peripheral blood/μL × 10^3 × blood volume processed in mL]) ×100.

- Simultaneously, a number of adverse incidents such as citrate toxicity, vasovagal reaction, allergic reaction, clot in the circuit, and flow issues were also noted in both the groups. Urine output and information related to coagulopathy were collected for all the patients and donors as well after 24 h
- Collection preference which determines the optimal positioning of interface for collection was adjusted by real-time monitoring of hematocrit and color of collected cells. The packing factor was kept default as per the Terumo BCT granulocyte apheresis protocol.

Statistical analysis

Data were recorded in a predesigned and pretested format. Statistical analysis was carried out using the Statistical Package for the Social Sciences (SPSS Inc., Chicago, IL, USA, version 23.0 for Windows). All quantitative variables were estimated using measures of central location (mean and median) and measures of dispersion (standard deviation and standard error). Donor parameters/procedure parameters were compared using parametric and nonparametric tests according to distribution (Shapiro–Wilk test) such as unpaired *t*-test or Mann–Whitney *U*-test.

Confidentiality of data and ethical clearance

Patients' data regarding the symptoms, disease, investigation, and treatment were accessible to the investigator and co-investigator and the institutional ethics committee only. Ethical clearance was obtained from the institutional ethical committee (Scientific Committee Approval No. Res/SCM/48/2021/129).

Granulocytapheresis

Granulocyte units were collected by continuous-flow apheresis (Spectra Optia, Terumo Penpol) with the use of a separation chamber and a collection chamber containing IDL or cMNC kits. The device interface offset detector was set between 45 and 50 to optimize granulocyte yield. ACD with NS and trisodium citrate, 35 mL of a 46.7% solution (trisodium citrate, Cytosol Laboratories, Braintree, MA), was added to a 500-mL bag of 6% HES (Volulyte 6%, Fresenius Kabi, GmBH, Germany).

The resulting ACD or citrate-containing HES solution was added continuously at a 1:12 ratio with whole blood to maintain anticoagulation and maximize granulocyte yield. The procedure ended when the bag of citrate-containing HES was completely infused, after approximately 5000–6000 mL of whole blood had been processed. Blood counts (Sysmex X-100, Transasia) were performed on samples collected from the donors immediately before and after donation and from the granulocyte concentrates before, during (for mid counts), and after gravity sedimentation.

Evaluation and comparison of the data from both the group was done for the following:

a. Whole blood processing (mL)
b. Duration (minute)
c. Anticoagulant used (donor and product mL)
d. Granulocyte product volume (mL)
e. Yield of the product (×10^{10}/unit)
f. Neutrophil yield of the product (×10^3/μL)
g. TLC of the product (×10^3/μL)
h. Platelet count of the product (×10^3/μL) and
i. Hematocrit (%) of the product.

Results

Donor characteristics and preharvest variables

The study included a total of 631 donors who underwent granulocyte apheresis procedure and were categorized into two groups, i.e., ACD (n = 292 from December 2015 to January 2019) and HES and trisodium citrate combination (n = 339 from February 2019 to September 2021). In the ACD group, apheresis was performed 10–12 h following mobilization by injection G-CSF and tablet dexamethasone. A similar protocol was undertaken in the HES and trisodium citrate combination group.

Both the groups were comparable in terms of median age (ACD = 29.5 vs. HES = 29), M: F ratio (ACD = 274/18 vs. HES = 330/09), median weight (ACD = 73 vs. HES = 74), preharvest neutrophil count (ACD = 32.14 × 10^3/μL vs. HES = 31.46 × 10^3/μL), preharvest WBC (ACD = 34.29 × 10^3/μL vs. HES = 33.57 × 10^3/μL), and preharvest platelet count (ACD = 247.5 × 10^3/μL vs. HES = 251 × 10^3/μL). The detailed donor demographics are provided in Table 1.

Postharvest product comparison

On Mann–Whitney *U*-test, a significantly better CE as well as product granulocyte yield was observed in the HES and trisodium citrate combination group. Both product neutrophil and granulocyte counts were also higher in HES donors, and also, less volumes of anticoagulant were required in the harvest [Figure 1 and Table 2]. The granulocyte concentrates were transfused after irradiation and labeling as per institutional protocol.

Discussion

Successful granulocyte harvests using HES as a red cell sedimenting agent are well known to separate granulocytes from red cells and to attain higher granulocyte yields.[4] HES 40 (high-molecular-weight [HMW] HES) mixed with trisodium citrate (as

Table 1: Demographic parameters of the donors

Donor parameters	ACD (*n*=292)	HES (*n*=339)	*P*
Age group (years) (range and median)	19–60 (29.5)	18–60 (29)	0.7163
Gender (male/female)	274/18	330/09	-
Weight (kg) (range and median)	50–120 (73)	51–114 (74)	0.7461
Preharvest neutrophil counts $\times10^3$/μL (median)	32.14	31.46	0.3279
Preharvest WBCs $\times10^3$/μL (median)	34.29	33.57	0.1899
Preharvest platelet counts $\times10^3$/μL (median)	247.5	251.0	0.4627

ACD=Acid citrate dextrose, HES=Hydroxyethyl starch, WBC=White blood count

Table 2: Granulocyte harvest details in the hydroxyethyl starch and acid citrate dextrose groups

Parameters	Comparison groups	Range	Median	Mean	SD	SEM	95% CI of median	*P*
Product neutrophil count ($\times10^3$/μL)	ACD	2.180–221.4	67.93	74.6	45.19	2.645	61.20–73.47	<0.0001
	HES	10.33–463.5	117.5	121.5	56.83	3.086	110.5–123.8	
Product WBC ($\times10^3$/μL)	ACD	9.7–247.2	81.06	88.68	48.09	2.814	73.12–86.91	<0.0001
	HES	16.91–494.1	132.6	136.4	59.84	3.250	123.8–139.8	
Product platelet count ($\times10^3$/μL)	ACD	92.0–2345	556.0	647.5	351.2	20.55	513.0–592.0	<0.0001
	HES	135–1033	358.0	375.6	125.1	6.796	346.0–369.0	
Product hematocrit (%)	ACD	2.2–50.3	6.58	9.641	9.072	0.5309	6.4–7.1	<0.0001
	HES	1.9–17.5	5.1	5.385	1.942	0.1055	4.9–5.4	
Product granulocyte yield ($\times10^{10}$/unit)	ACD	0.3–11.5	3.0	3.298	1.939	0.1135	2.7–3.3	<0.0001
	HES	1.0–10.1	4.5	4.5	1.699	0.0922	4.3–4.7	
Product volume (mL)	ACD	90.0–608	475	455.5	68.61	4.015	474.0–478.0	<0.0001
	HES	137–480	400	390.5	64.90	3.525	400.0–400.0	
WB processed (mL)	ACD	1194–9436	6055	6071	876.2	51.38	6001–6063	<0.0001
	HES	1952–6659	5112	5127	632.0	34.32	5105–5121	
Duration (min)	ACD	60–313	132	131.5	27.98	1.520	130.0–135.0	0.0122
	HES	38–240	125	128.1	29.18	1.708	121.0–129.0	
CE	ACD	1.306–43.91	14.70	15.86	8.464	0.4953	12.91–16.06	<0.0001
	HES	4.359–60.68	27.62	26.70	9.519	0.5170	26.28–29.17	
Total anticoagulant used	ACD	95–786	504	498.7	65.21	3.816	500–505	<0.0001
	HES	162–550	426	428.5	50.91	2.765	425–427	

SD=Standard deviation, SEM=Standard error of mean, ACD=Acid citrate dextrose, HES=Hydroxyethyl starch, WBC=White blood count, CI=Confidence interval, CE=Collection efficiency

an anticoagulant) was successfully used to facilitate the precipitation of red cells in granulocyte apheresis procedures.[11] However, HMW-HES may be potentially harmful to healthy donors because it was reported to cause severe side effects such as bleeding disorders, kidney failures, and impairment of hematopoiesis.[12-16] Therefore, several studies have suggested or reported an alternate option to HMW-HES. Studies done by Doblinger *et al*. and Dullinger *et al*. show that modified fluid gelatin derived by hydrolysis of collagen can serve as a sedimentation reagent for granulocyte harvest by apheresis, but it is associated with lower granulocyte yields.[17,18] Few other studies done by Thorausch *et al*. and Nanya *et al*. reported successful granulocyte apheresis harvest using MMW-HES,[19,20] which can also be used or administered safely as a plasma substitute.[13]

At our center, we planned to study to compare and analyze the benefits of granulocyte harvest apheresis procedures (Spectra Optia cell separator) using two different anticoagulant combinations such as ACD and 6% HES (a MMW HES) with 47.8% trisodium citrate mixture. There was no statistically significant difference in demographic parameters of both the groups, i.e. ACD and HES in terms of age, gender, and weight of participants/donors in our study. There was also no statistically significant difference in terms of premobilization (before injecting G-CSF and tablet dexamethasone) blood counts such as WBC, ANC, and platelet count.

In our study, there was no significant difference between the two groups in terms of preharvest ANCs, preharvest WBCs, and preharvest platelet counts. This is contrary to a study by Mandal *et al*.,[21] where they noted a significant difference between the two groups in terms of preprocedure ANCs (mean: 25,141.82/μL vs. 30,760.86/μL in the HES and non-HES groups, respectively). However, in their study, there was a difference between the onset of the procedure and mobilization which was 12 h in case of the non-HES group and 6–8 h in case of the HES group. The common gap of 12 h in our study for both procedures helped to eliminate this preharvest variable. Gatzemeier *et al*. also

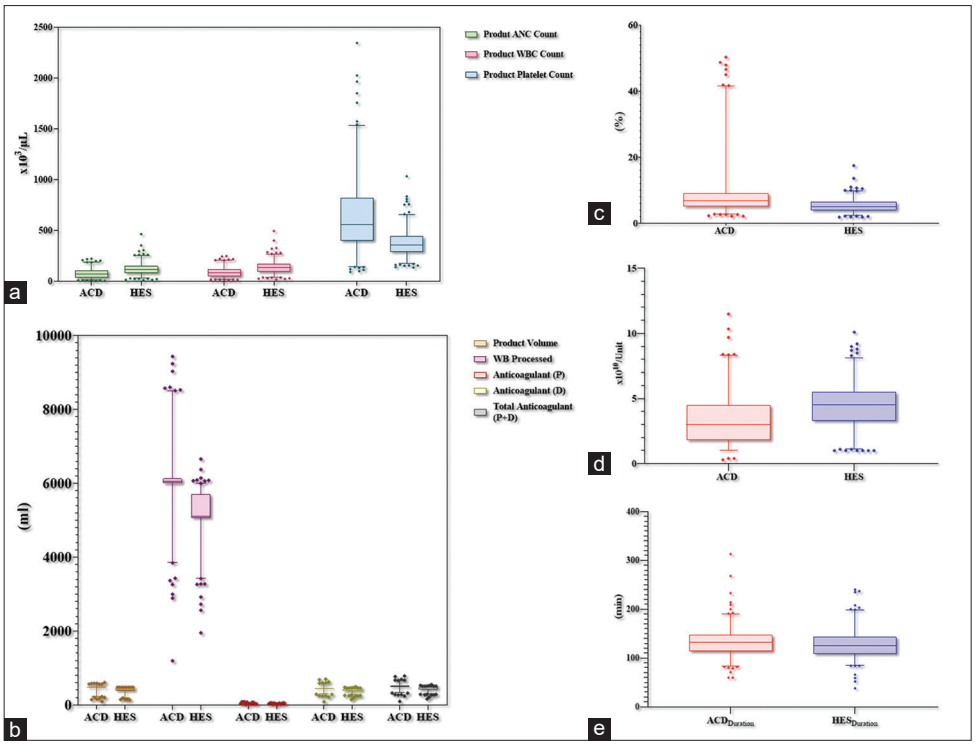

Figure 1: Granulocyte postharvest product details. (a) Product absolute neutrophil counts, white blood counts, and platelet counts. (b) Product volume, whole blood processed, and anticoagulant used in patients and donors. (c) Hematocrit (%). (d) Granulocyte harvest yields. (e) Procedure duration (minutes). ANC: Absolute neutrophil count, WBC: White blood count, ACD: Acid citrate dextrose, HES: Hydroxyethyl starch

reported that 12-h gap is a better time gap for G-CSF to reach its peak effect.[22]

In our study, postgranulocyte harvest parameters such as product yield, product neutrophil count, product WBC, product platelet count, and product hematocrit had a statistically significant difference between the two groups (ACD vs. HES). The HES group has better results in terms of product granulocyte yield, mean 3.29 × 10^{10}/unit versus 4.5 × 10^{10}/unit, $P \leq 0.0001$, in the ACD and HES groups, respectively; product neutrophil count, mean 74.6 × 10^3/µL versus 121.5 × 10^3/µL, $P \leq 0.0001$, in the ACD and HES groups, respectively; product WBC, mean 88.68 × 10^3/µL versus 136.4 × 10^3/µL, $P \leq 0.0001$, in the ACD and HES groups, respectively; product platelet count, mean 647.5 × 10^3/µL versus 375.6 × 10^3/µL, $P \leq 0.0001$, in the ACD and HES groups, respectively; and product hematocrit, mean 9.6% versus 5.3%, $P \leq 0.0001$, in the ACD and HES groups, respectively.

The CE in our study has a marked difference in both the groups (mean 15.86% vs. 26.70%, $P \leq 0.0001$, in the ACD and HES groups, respectively), which is due to processing of large amount of blood in the ACD group to achieve the yield. As a result, the time duration required to complete the procedure in the ACD group was statistically significantly higher than the HES group. The total anticoagulant used in harvest is also less in the HES group. Our results are comparable with other studies done using MMW-HES by Thorausch *et al*., Nanya *et al*., and Mandal *et al*.[19-21]

In this study, no adverse incidents, i.e., vasovagal reaction, citrate toxicity, clot in circuit, or poor/no blood flow, allergic reaction were noted in any of the groups. The urine output of donors and patients was unchanged in both the groups after donation or transfusion of the product. Donors and patients did not reveal any coagulopathy following the procedure or receiving the component till 24 h. This study shows that the granulocyte harvest by apheresis performed using HES (MMW) does not cause any complication among recipients and donors compared to normal one and it seems safe for use in the patients as well as the donor.

According to the recent articles and expert opinions, early GTX in the patient with sepsis resistant to primary line drug treatment may give a better outcome.[23,24] In these conditions, optimum granulocyte yield is very crucial, and to achieve a better yield, a minimum gap of 12 h between mobilization and collection is required.

At our oncology center, most of the neutrophil harvest requests are received from the hemato-oncology and BMT department. Voluntary donors for special procedures such as plateletpheresis and granulocyte apheresis are virtually negligible. Promising results from our study

such as significantly less blood volume processed and lesser duration of the procedure in the HES group can motivate the donors for voluntary donations. All these benefits can be achieved with minimal extra cost burden to the patient. The approximate consumable cost of granulocyte apheresis with ACD is INR 10,310/(cost included for 1 Spectra Optia kit, 1 ACD bag of 500 ml, and 2 16 g cannulas) and granulocyte harvest consumable cost with 6% HES (MMW) and trisodium citrate combination is INR 10,940/(cost included for 1 Spectra Optia kit, 1 6% HES bag of 500 ml and 7 trisodium citrate vials of 5 mL, and 2 16 g cannulas).

Conclusion

In our study, it is very obvious that granulocytes with optimum yield can be easily harvested with Spectra Optia cell separator using 6% HES (MMW) and trisodium citrate combination with standard 12-h interval gap between mobilization and harvest. In comparison to ACD anticoagulant used in granulocyte harvest, HES (MMW) with trisodium citrate strategy is very safe in terms of no adverse events as we can easily avoid citrate toxicity by not using ACD and also very effective in clinical practice. This strategy also has no or minimal extra cost burden to patients. The consumable cost of granulocyte harvest is minimally on a higher side in comparison to harvest with ACD (INR 10,940 vs. INR 10,310, respectively). Although we have analyzed a sufficient number of participants retrospectively, the data need further validated in prospective randomized controlled trial study.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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