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ORIGINAL RESEARCH

TRANSFUSION

Safety and efficacy of combined heparin/citrate anticoagulation for cell therapy collections in healthy adult allogeneic donors

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Abstract

Background: Reports on the safety and efficacy of combination heparin and citrate anticoagulation with cell therapy collections in adults are limited. There are no reports on the use of this combination in healthy allogeneic adult donors undergoing cell therapy collection. This retrospective analysis is the first study to examine its safety and efficacy in cell therapy collections of healthy adult allogeneic donors.

Study Design and Methods: The heparin infusion rate and adverse event profile for 90 cell therapy collections using 6 units heparin per mL of citrate anticoagulation were examined. In 12 consecutive large volume collections, activated partial thromboplastin time (aPTT), anti-Xa levels, and target cell collection efficiencies were also analyzed.

Results: Heparin infusion rates approximated the rate recommended for acute venous thrombosis. There were no adverse events related to heparin. There was a good correlation between aPTT and anti-Xa levels, but no patient had supratherapeutic and only 3 had therapeutic anti-Xa levels. An inverse correlation was found between the anti-Xa level and platelet loss. Collection efficiencies of mononuclear cell types were increased compared to citrate-only collections.

Conclusion: Heparin/citrate anticoagulation was safe, with lower heparin infusion rates, anti-Xa levels, and less prolonged aPTT than those observed in autologous adult donors. The good correlation between aPTT and anti-Xa levels suggests that aPTT levels can be used to estimate anti-Xa levels. Collection efficiencies of mononuclear cell types on heparin/ACD-A anticoagulation should be further explored.

KEYWORDS

anti-Xa, aPTT, citrate, hematopoietic progenitor cell collection, heparin, mononuclear cell collection

Abbreviation: FDA, Food and Drug Administration.

Jiahao Zhang and Minlin Wu are the co-first authors.

1 | INTRODUCTION

The number of allogeneic hematopoietic progenitor cell (HPC) transplants and interest in allogeneic immune effector cell therapy continue to grow, with such cell therapies most commonly collected by apheresis.[1,2] The most commonly used apheresis device is the Spectra Optia®,[3] for which the FDA-approved anticoagulant is Anticoagulant Citrate Dextrose Solution, Solution A (ACD-A). However, citrate toxicity frequently occurs with citrate anticoagulation, especially in patients with low total blood volumes (TBV) or undergoing large volume collections.[4,5] Up to 48% of patients undergoing large volume leukapheresis (LVL) for HPC collection experience symptoms of citrate toxicity.[6–8] Adverse reactions to citrate range from paresthesia and headache to life-threatening conditions such as arrhythmia and seizure.[8–11] In addition, calcium replacement requirements during HPC collection may lead to hypercalcemia that can require subsequent management. In one study, 76% of patients undergoing non-mobilized mononuclear cell (MNC) or HPC collections had post-apheresis ionized calcium levels above the upper limit of normal, especially with a high processing volume compared to donor weight.[12]

Heparin has been studied both as the sole anticoagulant and in combination with citrate, as adding heparin reduces the amount of citrate needed for anticoagulation. Heparin alone is associated with an increased risk of bleeding.[13] Heparin/ACD-A combinations typically use a ratio of 6–10 U heparin per mL of ACD-A,[14–18] with some adding extra ACD-A or heparin to the product bag.[15] The safety of this combination in children has been reported since the late 1990s,[13,19–22] where heparin has been more widely used than in adults due to children's slower metabolism of citrate,[23] lower antithrombin levels, and faster heparin metabolism.[24] Adults may be at higher risk of bleeding due to the apheresis anticoagulant rate being proportional to donor total blood volume, and of thrombosis due to heparin-induced thrombocytopenia (HIT), from previous exposure or possibly spontaneous.[8,25,26] Studies of heparin/citrate anticoagulation in adults are limited to those with cancer, with two studies reporting less citrate toxicity than with citrate alone, one reporting HIT, and none reporting bleeding[10,14,15,17,18,26] (Supplementary Table 1). Only one of these studies examined anticoagulation levels,[14] and to our knowledge, there have been no reports on anticoagulation levels in healthy adult allogeneic donors undergoing cell therapy collections with a heparin/ACD-A combination.

At New York Blood Center, we have performed LVL using 6 units/mL of ACD-A in healthy adult allogeneic donors collected through the National Marrow Donor Program (NMDP) since 2013. In this report, we describe the adverse event profile associated with our experience and in a subgroup of 12 consecutive donors, their blood anticoagulation levels and cell therapy product collection efficiencies.

2 | STUDY DESIGN AND METHODS

Adult NMDP donors who were treated with heparin/ACD-A anticoagulation between 2022 and 2025 were studied and compared to a contemporaneous cohort of adult NMDP donors treated with ACD-A anticoagulation only ($n = 114$). Donors were considered for a heparin protocol if their peripheral blood CD34+ count indicated that a LVL >5 TBV would be needed; if they had a TBV ≤5 L; or if they had symptoms of citrate toxicity. Contraindication to heparin was assessed during initial evaluation by donor services (allergies, medical history) and on the day of apheresis by the apheresis nurse (platelet count, interim history and physical exam). If the donor had a normal pre-procedure platelet count (150–400 K/μL) and no contraindication to heparin (e.g., allergy, high bleeding risk, history of HIT), then 6 U heparin/mL of ACD-A was added to the ACD-A bag.[10,14,15,17,18] Heparin 2000 units or 5% ACD-A by expected product volume was also sterilely added to the collection bag. Bleeding risk factors in this healthy donor population were considered to be a systolic blood pressure ≥160 mm Hg or recent major bleeding (other than menses). NMDP donors are instructed to avoid aspirin use, although our center allowed ibuprofen or naproxen for G-CSF related bony pain. Although the written informed consent did not specifically describe the risks of heparin, donors were verbally informed on the day of collection of the use of heparin.

Apheresis was performed using the continuous MNC procedure (version 11.3) of the Spectra Optia®, with a collect flow rate based on the MNC count as previously described[27,28] and a whole blood: anticoagulant ratio of 24:1. Intravenous (IV) calcium prophylaxis was given at 0.5 mg elemental calcium per mL of ACD-A. Complete blood counts were done using a D × H 520 hematology analyzer (Beckman-Coulter). MNC, lymphocyte, and monocyte CE1s and CD34+ CE2 were calculated as previously described.[28,29] Donors did not typically have follow-up laboratory monitoring when their platelet count was ≥50,000/μL upon procedure completion.

Twelve consecutive NMDP donors who underwent LVL collections (median 5.4, interquartile range (IQR) 4.6–6.2 TBV) also had a sample drawn immediately post-procedure to assess for supratherapeutic anticoagulation and excessive bleeding risk with this standard heparin

protocol: a blue top (sodium citrate) was drawn, immediately spun to obtain platelet-poor plasma, and frozen at −80°C a mean 1.8 ± 0.03 h after blood draw. Samples were stored for less than 6 months and then concurrently batch tested for activated partial thromboplastin time (aPTT) and heparin levels by a chromogenic anti-Xa assay using Hemosil Synthasil and Liquid Anti Xa reagents (Werfen, IL, USA), respectively, on the ACL TOP 750 analyzer device (Werfen, IL, USA).

To evaluate possible effects of the sodium citrate anticoagulant on the aPTT and anti-Xa level, heparin was neutralized in an aliquot of each plasma specimen with lyophilized heparinase (Dade Behring Hepzyme, Siemens Healthcare Diagnostics, Germany) as per manufacturer's instructions. Both the aPTT and anti-Xa assays were repeated post heparin neutralization. The aPTT reference range was 27.0–38.4 s, with the laboratory-validated therapeutic ranges for unfractionated heparin either 51.0–83.0 s or an anti-Xa level of 0.30–0.70 IU/mL.

All statistical analyses were conducted using Microsoft® Excel® for Microsoft 365 MSO (Version 2408 Build 16.0.17928.20066). Descriptive characteristics indicate the median and IQR. Appropriate *T*-testing and ANOVA with post-hoc testing were performed after testing for unequal variances.

3 | RESULTS

A total of 90 NMDP donors were available for analysis (Table 1), of which 86 were HPC donors and 4 were non-mobilized MNC donors. Regarding the indications for a heparin protocol, 71% had >5 TBVs processed; 67% had a TBV ≤5 L; and 17% had citrate toxicity which prompted switching to a heparin protocol. Their median donor TBV was 4511 mL (IQR 3102–5921 mL); median number of TBVs processed was 5.63 (IQR 4.31–6.95), and the median whole blood volume processed was 25,000 mL (IQR 17,792–32,209 mL). The median heparin infusion rate was 16.8 U per kilogram of donor body weight per hour (IQR 10.7–22.9 U/kg/h), with an estimated median duration of heparin infusion of 319 min (IQR 246–392 min). The anticoagulation infusion rate was significantly lower (p <.0001) than that of our ACD-only collections, with a median of 0.73 (IQR 0.6–0.85) compared to 0.9 (IQR 0.8–0.9) mL/min/L TBV.

Ten donors experienced an adverse event during apheresis; 9 donors had CTCAE (Common Terminology Criteria for Adverse Events) Grade 2 citrate toxicity resolved with IV calcium gluconate and 1 donor had issues with venous access (collapsing vein). No donor had prolonged bleeding with peripheral IV removal. No clumping or clotting of the circuit or in the cell therapy product occurred. No adverse events were deemed heparin-related (e.g., bleeding, heparin-induced thrombocytopenia) either during the procedure or on minimum 6-month follow-up of NMDP donors. There was no significant correlation between the heparin infusion rate and platelet loss (Figure 1). The platelet loss per # TBV processed was significantly lower (p <.0001) than that of our ACD-only collections, with a median of 20.6 (IQR 16.6–25.3) compared to 31.5 (IQR 23.3–42.6).

Twelve consecutive NMDP donors who underwent LVL had post-apheresis anticoagulation levels assayed (Table 2), to assess for supratherapeutic anticoagulation and excessive bleeding risk with this standard heparin

TABLE 1 Donor and procedure characteristics (n = 90).

Donor	Median age (years)	27 (IQR 20–35)
	Gender (male/female/other)	42/48/1
	Median body weight (kg)	73 (IQR 52–94)
	Median TBV (mL)	4511 (IQR 3102–5921)
Procedure	# TBVs processed	5.63 (IQR 4.31–6.95)
	WBV processed (mL)	25,000 (IQR 17792–32,209)
	AC infusion rate (mL/min/L TBV)	0.73 (IQR 0.48–0.98)
	Heparin infusion rate (U/kg/h)	16.8 (IQR 10.7–22.9)
	Heparin infusion duration	319 (IQR 246–392)
	Total # adverse events	10 (described in text)

Abbreviations: AC, anticoagulant; TBV, total blood volume; WBV, whole blood volume.

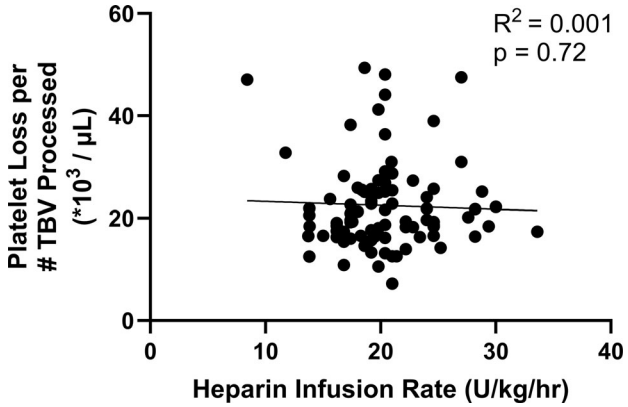

FIGURE 1 Linear regression analysis between platelet loss and heparin infusion rate. Each donor's platelet loss per number of TBVs processed is plotted against their respective heparin infusion rates, and the correlation between the two variables is insignificant at $R^2 = 0.001$ ($p = .72$).

TABLE 2 Anticoagulant levels and collection efficiencies in 12 consecutive donors undergoing large-volume leukapheresis.

Donor	Anti-Xa (IU/mL) (0.3–0.7 therapeutic)	Hepzyme anti-Xa (IU/mL)	aPTT (s) (27–38.4 normal)	Hepzyme aPTT (s)	MNC CE1	Lymphocyte CE1	Monocyte CE1	CD34 CE2
1	0.41	0.08	69.7	33.7	1.12	1.09	1.20	0.85
2	0.11	0.05	35.4	31.1	0.46	0.45	0.46	0.39
3	0.08	0.01	42.3	34.5	1.12	1.06	1.18	0.90
4	0.24	0.03	52.2	32.8	0.76	0.78	0.75	0.52
5	0.04	0.03	34.1	36.2	0.91	0.89	0.93	0.76
6	0.23	0.05	50.3	34.8	0.91	0.73	1.30	0.69
7	0.41	0.06	74.5	36.9	0.78	0.70	0.89	0.58
8	0.22	0.04	43.2	33	0.71	0.67	0.75	0.49
9	0.26	0.05	45.5	29.2	2.01	1.75	2.44	0.47
10	0.23	0.06	39.4	29.6	1.03	1.09	0.88	0.58
11	0.26	0.06	47.2	30.9	0.66	0.66	0.64	N/A[a]
12	0.42	0.03	106.5	39	0.85	0.73	1.79	N/A[a]

[a]2 donors underwent non-mobilized MNC (mononuclear cell) collection and therefore did not have CD34 CE2 data.

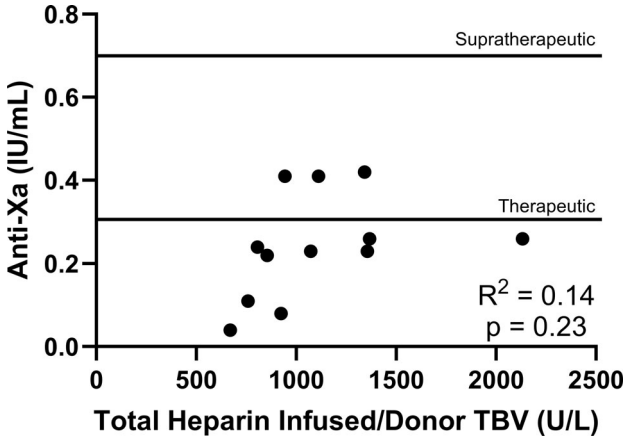

FIGURE 2 Anti-Xa levels in 12 consecutive donors of large volume leukapheresis (LVL). The donors' anti-Xa levels following the LVL procedure are plotted against the total heparin infused into each donor normalized by donor TBV, and the correlation between the two variables is insignificant at $R^2 = 0.14$ ($p = .23$). All donors' anti-Xa levels remained below supratherapeutic ranges, with only 3 out of 12 donors having therapeutic levels of anti-Xa.

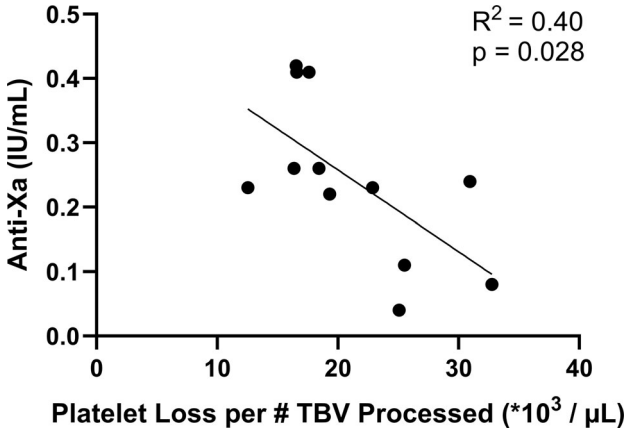

FIGURE 3 Linear regression analysis between donor anti-Xa levels and platelet loss following LVL. The donors' anti-Xa levels post-LVL had a moderate but statistically significant negative correlation with their platelet loss per number of TBV processed ($R^2 = 0.40$, $p = .028$).

protocol. Their median anti-Xa level was 0.24 IU/mL (IQR 0.13–0.34 IU/mL), with 3 donors demonstrating anti-Xa levels in the therapeutic range of 0.3–0.7 IU/mL and no donors having anti-Xa levels in the supratherapeutic range (Figure 2). There were no significant correlations between anti-Xa levels and the total heparin infused normalized by donor TBV (Figure 2) or the heparin infusion rate (data not shown). Interestingly, there was a moderate correlation ($R^2 = 0.40$, $p = .028$) between the anti-Xa level and platelet loss (Figure 3), with higher anti-Xa levels having less platelet loss (Figure 3). The median aPTT was 46.4 s (IQR 31.4–61.4 s), with a highly significant linear correlation between aPTT and anti-Xa activity (Figure 4; $R^2 = 0.69$, $p > .001$). As with anti-Xa, there was no correlation between the aPTT level and the heparin infusion rate. Treatment of donor blood samples with Hepzyme to rule out any citrate anticoagulation effects reverted all donor anti-Xa levels to subtherapeutic range (Supplemental Figure 1) and reverted all but the most anticoagulated donor's aPTT level to normal range (Table 2).

The median CE1s for all 12 donors was 0.88 (IQR 0.58–1.19) for MNC, 0.76 (IQR 0.38–1.13) for lymphocytes, and 0.91 (IQR 0.44–1.38) for monocytes. For the

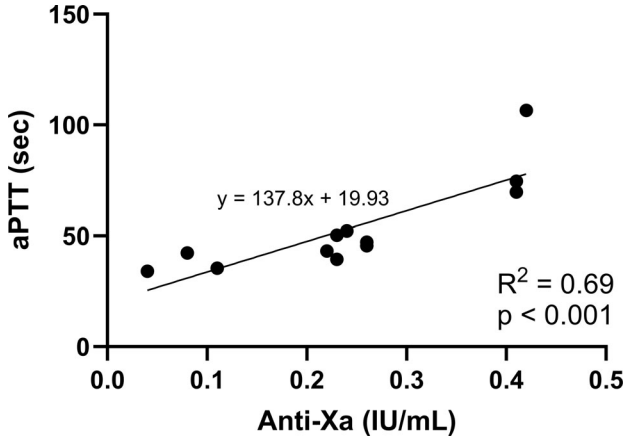

FIGURE 4 Linear regression analysis between donor aPTT and anti-Xa levels following LVL. The donors' anti-Xa levels and aPTTs post-LVL had a strong and significant correlation with each other ($R^2 = 0.69$, $p < .001$).

10 donors who underwent HPC collection, the median CD34 CE2 was 0.58 (IQR 0.33–0.83). The medians and IQRs are shown in Table 3, along with data on our ACD-only collections for HPC ($n = 90$) and non-mobilized MNC products ($n = 24$). There was no significant difference in CD34 CE2 between the heparin/ACD and ACD-only collections, but the CE1s for MNC, lymphocytes, and monocytes were significantly higher with the heparin/ACD combination.

4 | DISCUSSION

This study is the first to investigate the safety of combined heparin/citrate anticoagulation with cell therapy collection procedures in healthy adult allogeneic donors, as previous studies involved adults with underlying malignancies or pediatric donors. The addition of heparin reduces the risk of citrate toxicity but has been used less frequently in adults due to potential risks of bleeding (anticoagulant rate being proportional to donor total blood volume) and of heparin-induced thrombocytopenia from previous heparin exposure or possibly spontaneous.[8,25,26]

Our study provides evidence for the safety of infusing 6 U heparin per mL ACD-A for apheresis anticoagulation, which resulted in a median heparin infusion rate of 17 U/kg/h, similar to the standard 18 U/kg/h maintenance for venous thrombosis[30] and lower than that reported in autologous donors.[14] The indication for using the heparin protocol in most donors was a LVL >5 TBV; notably, 80% of donors with a TBV ≤5 L had >5 TBV processed. The anticoagulation infusion rate was significantly lower ($p < .0001$) than that of our ACD-only collections, suggesting achievement of a lower fluid balance with the use of a heparin protocol.

Ten non-heparin-related side effects occurred across 90 donor observations, 9 of CTCAE Grade 2 citrate toxicity resolved with IV calcium gluconate, for an overall citrate toxicity rate of 10%. We routinely administer IV calcium prophylaxis and notably, our citrate toxicity rate is lower than the 20% rate reported in healthy allogeneic HPC donors on citrate-only anticoagulation receiving calcium prophylaxis[6] and also lower than the 39% rate reported in autologous adult HPC donors anticoagulated with heparin/ACD-A where the calcium prophylaxis strategy was not described.[10] NMDP donors who were collected up to September 2015 (we started using a heparin protocol in 2013) underwent long-term follow-up by NMDP and no increase in thrombotic adverse events was reported.[31] In addition, although our institution does not have our own explicit protocol to monitor donors longitudinally, NMDP follows all donors closely out to 6 months post-transplant. In the 90 donors analyzed, there was no correlation between platelet loss and heparin infusion rate, and platelet loss was significantly decreased compared to that of our ACD-only collections. Consistent with this, in the 12 LVL donors where anti-Xa levels were analyzed, platelet loss with cell therapy collection was less with higher anti-Xa levels. We hypothesize that this reduced platelet loss may be related to decreased platelet activation due to heparin's anti-P- and anti-L-selectin activity.[32,33] Platelet clumping was not noted in any procedures, in contrast to the report of 63% of collections with platelet clumping in autologous donors collected on a similar heparin protocol.[17] In that study, however, platelet clumping was associated with a lower white cell count, suggesting its association with hematopoietic recovery.

The coagulation assays further reflect this heparin protocol's safety in healthy adult allogeneic donors, as no clotting in the apheresis circuit or cell therapy product occurred with a median anti-Xa level of 0.24 IU/mL. Notably, the level of anti-Xa activity required to reduce clotting in extracorporeal membrane oxygenation has been found to be at least 0.25 U/mL.[34] Only 3 donors of 12 LVL donors reached therapeutic levels of anti-Xa (0.3–0.7 IU/mL) and 4 of the 12 donors had aPTT levels in the therapeutic range (51–83 s), consistent with reports that therapeutic aPTT levels can be associated with anti-Xa levels below the therapeutic range.[35,36] Notably, our median anti-Xa and aPTT levels of 0.24 (IQR 0.13–0.34 IU/mL) and 46.4 (IQR 31.4–61.4) s were lower than that reported in autologous adult HPC donors with cancer, where the median anti-Xa and aPTT levels were 0.69 (range, 0.10–1.29) IU/mL and 70 (range, 44–100) s, respectively.[14] We also had no donors with

TABLE 3 Target cell collection efficiencies with heparin/ACD compared to ACD-only collections.[a]

Donor category	CD34+ CE2	MNC CE1	Lymphocyte CE1	Monocyte CE1
LVL donors ($n = 10–12$)	0.58 (0.33–0.83)	0.88 (0.58–1.18)	0.76 (0.38–1.13)	0.91 (0.44–1.38)
ACD-only HPC donors ($n = 90$)	0.59 (0.43–0.74)	0.25 (0.26–0.44)	0.49 (0.30–0.69)	0.25 (0.15–0.36)
ACD-only MNC donors ($n = 24$)	N/A	0.69 (0.52–0.86)	0.66 (0.43–0.90)	0.62 (0.31–0.94)
p-value (*t*-test/ANOVA)	0.56	<0.0001	<0.0001	<0.0001
p-value (Games–Howell, LVL donors vs. ACD-A only HPC donors)	N/A	<0.001	0.005	<0.001

Abbreviations: HPC, hematopoietic progenitor cell; LVL, large volume leukapheresis; MNC, mononuclear cell.
[a]Values represent median (IQR).

supra-therapeutic anti-Xa levels compared to their 27% of donors. We hypothesize that these differences may be related to higher heparin metabolism and higher weight of healthy allogeneic donors compared to autologous donors with cancer.

Anti-Xa and aPTT levels normalized upon Hepzyme treatment, confirming the minimum effects of the citrate anticoagulation on their levels. There was a good correlation between the anti-Xa and aPTT levels, with a notably higher correlation ($R^2 = 0.69$) than that observed in adult HPC patients with cancer ($R^2 = 0.14$),[14] suggesting that, although anti-Xa is preferable as the more accurate assay,[36] less costly aPTT levels can be reflective of anti-Xa levels in healthy adult allogenic donors.

Finally, in the 12 donors analyzed, our median CD34+ CE2 of 0.58 was similar to that observed with ACD-only anticoagulation, which agrees with one report[18] but not with another report finding higher CD34+ CE with the combination.[37] Interestingly, our median CE1s for MNC, lymphocytes, and monocytes were significantly higher than our ACD-only CEs for both HPC and non-mobilized MNC collections, which is consistent with a single case report where heparin/ACD-A was compared to ACD-A only for MNC CE1.[38] Given the small number of donors studied, further studies comparing MNC CEs with heparin-containing versus citrate-only anticoagulation need to be done, but data so far indicate that CEs do not appear to be adversely affected by the addition of heparin anticoagulation.

In summary, this first-time study in healthy allogeneic donors of adverse events, anticoagulation levels, platelet loss, and collection efficiencies associated with the use of heparin/ACD-A anticoagulation supports the safety and efficacy of this combination. All donors before being placed on heparin/citrate anticoagulation, however, should be queried about risk factors for bleeding or HIT, with appropriate risk management, including describing the risks of heparin administration in the written consent form for cellular therapy collection.

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CONFLICT OF INTEREST STATEMENT

There are no conflicts of interest for any of the authors.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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