Received: 21 December 2024 | Revised: 17 March 2025 | Accepted: 27 April 2025

DOI: 10.1111/trf.18280

TRANSFUSION

ORIGINAL RESEARCH

Transfusion Practice

Novel method of leukocytapheresis using a highly concentrated sodium citrate solution alternative to acid citrate dextrose solution A

Masaya Abe[1] | **Keiko Fujii**[2,3] | **Toshiharu Mitsuhashi**[4] | **Wataru Kitamura**[1] | **Kazuhiro Ikeuchi**[1] | **Takuya Fukumi**[1] | **Kana Washio**[5] | **Fumio Otsuka**[2,6] | **Yoshinobu Maeda**[3] | **Nobuharu Fujii**[1,3]

[1]Division of Transfusion and Cell Therapy, Okayama University Hospital, Okayama, Japan

[2]Division of Clinical Laboratory, Okayama University Hospital, Okayama, Japan

[3]Department of Hematology and Oncology, Okayama University Hospital, Okayama, Japan

[4]Center for Innovative Clinical Medicine, Okayama University Hospital, Okayama, Japan

[5]Department of Pediatric Hematology and Oncology, Okayama University Hospital, Okayama, Japan

[6]Department of General Medicine, Dentistry and Pharmaceutical Sciences, Okayama University Graduate School of Medicine, Okayama, Japan

Correspondence
Keiko Fujii, Division of Clinical Laboratory, Okayama University Hospital, 2-5-1 Shikata-cho, Kita-ku, Okayama 700-8558, Japan.
Email: keikofujii@s.okayama-u.ac.jp

Abstract

Background: Large-volume leukocytapheresis is time consuming. The upper limit of the inlet flow rate is determined by the inlet: anticoagulant (AC) ratio and can be changed by combining the AC with heparin. Here, we devised a protocol to increase the AC ratio using a highly concentrated sodium citrate solution without heparin.

Study Design and Methods: We collected data from 40 consecutive apheresis procedures performed using the Spectra Optia system on 40 donors for allogeneic peripheral blood stem cells between June 2022 and June 2023. We used AC containing 2.2% sodium citrate (normal concentrated sodium citrate [NSC]) and 5.32% sodium citrate (highly concentrated sodium citrate [HSC]). The AC ratios were set to 12:1 and 24:1 for the NSC and HSC, respectively.

Results: The processed volume was not different; the maximum inlet flow rate increased, the total processing time was reduced, the AC solution used was reduced, and the product volume was reduced in the HSC group, compared to the NSC group. Although the CD34+ cell CE2 was reduced in the HSC group,

Abbreviations: AC, anticoagulant; ACD-A, acid citrate dextrose solution A; AIPW, augmented inverse-probability weighting; ATE, average treatment effect; CE, collection efficiency; HES, hydroxyethyl starch; HLA, human leukocyte antigen; HSC, high sodium citrate concentration; MNC, mononuclear cell; NSC, normal sodium citrate concentration; PB, peripheral blood; PBSC, peripheral blood stem cell; TBV, total blood volume; WBC, white blood cell.

no difference was observed in the number of collected CD34+ cells. The incidences of citrate-related reactions were similar.

Discussion: We propose a novel leukocytapheresis method using HSC that shortens the procedure time and reduces the amount of AC solution used compared to the conventional method.

KEYWORDS

anticoagulant, apheresis, high sodium citrate concentration, Spectra Optia

1 | INTRODUCTION

Peripheral blood stem cell (PBSC) transplantation and chimeric antigen receptor T (CAR-T) cell therapy require harvesting mononuclear cells (MNCs) using centrifugal apheresis systems.[1] Platelets are activated by physical contact with the tube used for extracorporeal circulation, and the coagulation system is accelerated, leading to blockage of the extracorporeal circulation circuit.[2] An anticoagulant (AC) is required to prevent clotting of the extracorporeal circuit and collected blood products. Citric acid has long been used as an AC[3] and is suitable for blood additives and extracorporeal circuits with low blood flow rates (30–70 mL/min).[2] Citrate exerts its AC effect by reversibly chelating divalent cations, such as calcium and magnesium, and inhibiting the normal physiological functions of these ions. However, when citrate-containing blood is returned to the patient and donor, cation chelation may continue in the systemic circulation.[2] Consequently, metabolic complications, including hypocalcemia, hypomagnesemia, metabolic alkalosis, and other electrolyte abnormalities occur, leading to citric acid-related reactions.[2,4–6]

According to the information provided by the manufacturer for the centrifugal blood component separator Spectra Optia (Terumo BCT, Inc., Lakewood, CO, USA), in a continuous MNC collection program, it is assumed that acid citrate dextrose solution A (ACD-A) will be used as an AC, and that the whole blood to AC ratio (hereafter referred to as the AC ratio) will be set from 6:1 to 15:1. The inlet flow rate is determined using the following formula: inlet flow rate (mL/min) = AC injection rate (mL/min/L total blood volume [TBV]) × TBV (L) × AC ratio + AC to collection bag (mL/min). If the procedure time is prolonged owing to large-volume leukocytapheresis, problems such as citric acid accumulation and fluid retention may occur owing to large amounts of ACD-A, and apheresis may take several days. If the patient's condition permits, the inlet flow rate is gradually increased to shorten the procedure time.[7] However, the inlet flow rate eventually reaches the upper limit. To deal with the limit of the inlet flow rate by the device, a method using heparin as the AC has been devised. Using heparin, the AC ratio and inlet flow rate can be increased, which can also reduce the volume load caused by AC.[2,8,9] However, the use of heparin as AC is prohibited when harvesting CAR-T cell products other than tisagenlecleucel.

In this study, we investigated a method to increase the inlet flow rate by changing the AC ratio without heparin. We focused on ACD-A at a concentration of 2.2% sodium citrate solution. We devised a new method to increase the concentration of sodium citrate solution used in the AC up to 5.32% and initiate apheresis with an AC ratio of 24:1. Additionally, we retrospectively analyzed apheresis using standard and high sodium citrate concentrations (HSCs) and verified the safety and effectiveness of the new apheresis method.

2 | STUDY DESIGN AND METHODS

2.1 | Donors

This retrospective study included donors between June 2022 and June 2023 who underwent leukocytapheresis in Okayama University Hospital. HSC was available in the leukocytapheres after November 2022. We retrospectively extracted data from medical records. The healthy donors aged 15–65 years received allogeneic PBSC harvests. The PBSCs from all donors were mobilized using granulocyte colony-stimulating factor alone. This retrospective analysis was performed in accordance with the Declaration of Helsinki and approved by the Certified Review Board of Okayama University. The requirement for informed consent was waived by the Certified Review Board due to the retrospective design of the study, which used aggregated and anonymized medical information. In addition, study-related information was published on the institute's website, and all the participants were provided the opportunity to opt out.

2.2 | Preparation of anticoagulants

In the normal sodium citrate concentration (NSC) group, ACD-A solution (Terumo Corporation, Tokyo, Japan) alone was used as the AC, and the sodium citrate concentration was 2.2%. In the HSC group, a mixed solution of

ACD-A solution and 10% sodium citrate hydrate (Fuso Pharmaceutical Industries, Osaka, Japan) was used as an AC, and the citric acid concentration was 5.32%. To prepare the composition, 300 mL of ACD-A solution and 200 mL of 10% sodium citrate hydrate were mixed.

2.3 | Apheresis procedure for harvesting peripheral blood stem cells

PBSCs were harvested using the two-needle method with a continuous cell separator (Spectra Optia). Harvesting was performed using a continuous MNC collection program. The processed blood volume (ranging from 150 to 300 mL/kg) was determined to be sufficient to obtain the required number of CD34+ cells in 1 day if possible. Predictive algorithms were used to calculate the processed blood volume to ensure the target CD34+ cell yield. The factors included the pre-CD34+ cells, recipient body weight, and degree of human leukocyte antigen (HLA) matching. The target CD34+ cell yield was calculated to ensure a minimum of 2×10^6 cells per recipient body weight in HLA-matched donors, and a minimum of 4×10^6 cells per recipient body weight in HLA-haploidentical donors. For cases involving PBSC collection on ≥2 consecutive days, only the data from the first day were analyzed in this study. All donors received continuous intravenous administration of calcium gluconate hydrate (Nichi-Iko Pharmaceutical Co., Ltd., Toyama, Japan) to prevent adverse citrate-related reactions. The whole blood-to-AC ratio (inlet: AC ratio) was initially set to 12:1 in the NSC group and 24:1 in the HSC group. The AC injection rate was initially set at 0.8 in both groups. The packing factor was set to 4.0.

2.4 | Collection efficiency analysis

The collection efficiency (CE) can affect the results of apheresis, in addition to the target cell count in the peripheral blood (PB) and the processed volume.[10] CE2 is commonly used to measure collection performance[11]; we analyzed CE2 using the following formula: apheresis yield/(cell $\text{count}_{\text{PB pre-apheresis}} \times$ total processed volume) $\times$ 100 (%).

2.5 | Evaluation of citrate-related reactions

Experienced doctors assessed citrate-related reactions, such as perceptual abnormalities, convulsions, and nausea. The reactions were graded according to the method described by Bolan et al.[12] Physicians assigned a grade of "0" if no symptoms were observed, "1" if symptoms were barely observed (mild dysesthesia), "2" if symptoms were irritating (moderate dysesthesia), "3" if symptoms were unpleasant (severe dysesthesia, nausea, irritability, and anxiety), and "4" if symptoms were unbearable (arrhythmia, tetany, and seizures).[13]

2.6 | Assessment of platelet changes after apheresis

Blood tests were performed before and after apheresis. Platelet counts were compared, and the percentage decrease was calculated using the following formula: $([\text{Platelet}_{\text{PB pre-apheresis}} - \text{Platelet}_{\text{PB post-apheresis}}]/\text{Platelet}_{\text{PB pre-apheresis}}) \times 100$ (%).

2.7 | Statistical analyses

The mean ± standard deviation is reported, unless otherwise noted. Fisher's exact test and the independent samples *t*-test were used to compare the two groups. To eliminate the effects of confounding factors and examine the impact of HSC on the procedure time, we adjusted for the effect of HSC using augmented inverse-probability weighting (AIPW) and calculated the potential outcomes and average treatment effect (ATE). AIPW is a statistical model that is doubly robust due to the combination of an outcome model and a treatment model. The potential confounders were sex, age, body mass index, TBV, white blood cell (WBC) count, hematocrit, pre-apheresis platelet count, pre-CD34+ cell count, target CD34+ cell yield, and maximum inlet flow rate. In the AIPW outcome model, all confounders were applied. However, in the treatment model, complete separation occurred when all confounders were applied, and it was impossible to perform the calculation. Therefore, a model excluding the maximum inlet flow rate was used. The strength of the correlation was determined by the absolute *r* value for each evaluation using Pearson's correlation coefficient. Statistical analyses were performed using GraphPad Prism 8 (GraphPad Software, San Diego, CA, USA) and Stata 18/MP8 (StataCorp, College Station, TX, USA). Two-tailed *p* values <.05 were considered significant.

3 | RESULTS

3.1 | Allogeneic peripheral blood stem cells harvested from the donors

Table 1 summarizes the information for the allogeneic PBSCs harvested from the donors. Twenty-eight donors underwent apheresis using NSC as the AC, and 12 donors

TABLE 1 Characteristics of the donors who underwent allogeneic peripheral blood stem cell harvesting.

	Normal	High	*p* Values
Clinical characteristics			
Number	28	12	
Age[a]	38.5 (18–65)	39.5 (22–56)	.87
Sex (male/female)	21/7	6/6	.15
Body weight (kg)[a]	67.7 (44.7–98.6)	66.7 (47.0–90.2)	.78
TBV (mL)	4423 ± 732	4375 ± 839	.85
HLA (matched/haploidentical)	15/13	1/11	.01
Pre-apheresis laboratory variables			
WBC count ($\times 10^9$/L)	42.4 ± 7.1	46.3 ± 10.0	.17
MNC count ($\times 10^9$/L)	5.1 ± 1.6	6.1 ± 1.3	.047
CD34+ cell count ($\times 10^6$/L)	46.6 ± 27.7	63.2 ± 37.7	.13
Hct (%)	43.7 ± 3.0	42.5 ± 3.6	.27
Pre-apheresis PLT count ($\times 10^9$/L)	217.2 ± 34.9	190.3 ± 43.5	.044
Target CD34+ cell yield ($\times 10^6$ cells)	171.9 ± 87.3	228.9 ± 82.3	.06
Leukocytapheresis variables			
AC ratio at the end (X:1)	13.0 ± 0.4	26.4 ± 1.0	<.0001
AC injection rate at the end (mL/min/L TBV)	1.26 ± 0.11	0.82 ± 0.07	<.0001
Processed blood volume (mL)	12,980 ± 3090	12,799 ± 3262	.87
Maximum inlet flow rate (mL/min)	70.6 ± 10.4	86.2 ± 15.2	.0005
Procedure time (min)	227 ± 49	194 ± 43	.049
Total amount of AC (mL)	1080 ± 260	519 ± 127	<.0001
Leukocytapheresis outcomes			
Product volume (mL)	213.1 ± 47.5	176.6 ± 39.9	.025
Sodium citrate concentration in product (%)	0.29 ± 0.02	0.34 ± 0.04	<.0001
Total CD34+ cell yield ($\times 10^6$ cells)	311.2 ± 155.6	298.2 ± 128.8	.80
CD34+ cells/recipient body weight (10^6 cells/kg)	5.89 ± 3.86	7.05 ± 8.72	.56
CD34+ cell CE2 (%)	55.4 ± 10.2	43.3 ± 17.1	.0086
PLT yield ($\times 10^9$)	407.1 ± 112.0	353.3 ± 122.8	.18
PLT loss (%)	37.8 ± 7.9	34.8 ± 10.4	.33
Ionized calcium (mmol/L)	1.10 ± 0.08	1.06 ± 0.06	.20
Potassium (mmol/L)	3.41 ± 0.17	3.51 ± 0.22	.14
Magnesium (mg/dL)	1.59 ± 0.14	1.68 ± 0.15	.06
Citrate toxicity, number (%)	5 (18.5)	2 (16.7)	>.99

Note: Values represent the mean ± standard deviation.

Abbreviations: AC, anticoagulant; CE, collection efficiency; Hct, hematocrit; HLA, human leukocyte antigen; MNC, mononuclear cell; PLT, platelet; TBV, total blood volume; WBC, white blood cell.

[a]The data are shown as median and range.

underwent apheresis using HSC. No significant differences were observed between the NSC and HSC groups in terms of donor age, sex, body weight, and TBV. However, in the HSC group, there were more HLA-haploidentical donors, and the target CD34+ cell yield tended to be larger. In the pre-apheresis tests, there was a difference in the MNC and platelet counts. The apheresis results showed differences between the AC ratio and AC injection rates. Although no difference was observed in the processed blood volume, there was a difference in the maximum inlet flow rate, leading to a shorter total procedure time for HSC apheresis. The total amount of AC was lower in the HSC group. There were also differences in the product of volume and final sodium citrate

concentration. Although there were no differences in the pre-apheresis CD34+ count, total collected CD34+ cells, or collected CD34+ cells/recipient body weight, a significant difference was observed in the CD34+ cell CE2. There were no differences in the platelet yield in the product and the rate of decrease in platelets, and there were no differences in ionized calcium, potassium, and magnesium after apheresis. Moreover, there were no differences in citrate-related reactions. In the NSC group, four donors developed a grade 1 citrate-related reaction, and one developed a Grade 2 citrate-related reaction. In the HSC group, one developed a Grade 1 reaction, and one developed a Grade 2 reaction. No grade three or higher reactions were observed in either group.

3.2 | Augmented inverse-probability weighting estimation of the potential outcomes and average treatment effect

We investigated the effects of shortening the procedure time for allogeneic PBSC harvesting. As presented in Table 2, the potential outcome calculated by AIPW was 227.5 and 188.5 min for NSC and HSC, respectively. The ATE was −39.0 min, which was statistically estimated to be effective in shortening the procedure time.

3.3 | Correlations among allogeneic peripheral blood stem cells harvesting data

We evaluated the correlation among allogeneic PBSC harvesting data (Table 1). The NSC group demonstrated a moderate positive correlation between the CD34+ cell CE2 and maximum inlet flow rate, whereas the HSC group tended to have a moderate positive correlation (Figure 1A). The NSC group demonstrated a moderate positive correlation between the CD34+ cell CE2 and TBV; however, the HSC group showed no such correlation (Figure 1B). In the NSC group, there was a strong positive correlation between the maximum inlet flow rate and TBV, whereas the HSC group showed a moderate positive correlation (Figure 1C). There was also a weak negative correlation between the CD34+ cell CE2 and pre-apheresis WBC count in the NSC group, but no correlation was observed in the HSC group (Figure 1D). There was no correlation between the CD34+ cell CE2 and pre-apheresis MNC or CD34+ cell counts in the NSC and HSC groups (Figure 1E,F).

4 | DISCUSSION

Granulocyte collection using the Spectra Optia system requires hydroxyethyl starch (HES) to promote red blood cell sedimentation with the addition of sodium citrate as an AC. We previously reported the collection of granulocytes using varying concentrations of HES and sodium citrate. For granulocyte collection, it was efficient to reduce the AC concentration and increase the amount of HES infused to promote red blood cell sedimentation and granulocyte separation.[14] Conversely, when collecting MNCs, it is necessary to reduce the injection of large amounts of ACD-A; therefore, we investigated methods for concentrating the AC.

Since 46.7% trisodium citrate was not available in Japan, HSC was prepared using 10% sodium citrate. In the novel method, we set the AC ratio to twice the normal ratio. Since this was a pilot method, platelet aggregation and coagulation had to be minimized. Therefore, the concentration of sodium citrate in HSC was slightly higher than twice that of NSC. In other words, a new method was devised to prepare a highly concentrated sodium citrate solution by adding 10% sodium citrate to ACD-A, changing the AC ratio to 24:1.

In this study, we compared allogeneic PBSC apheresis using citric acid (normal or high concentration) as the AC solution, performed using the Spectra Optia system at a single institution. Our findings demonstrated that collecting allogeneic PBSCs using HSC as the AC increased the maximum inlet flow rate, shortened the total processing time, reduced the total amount of AC solution, and reduced the product volume compared with the use of NSC as the AC. Although previous studies have reported

TABLE 2 Results of the augmented inverse-probability weighting estimation of potential outcomes and the average treatment effect in allogeneic peripheral blood stem cells harvested from donors.

	Sodium citrate concentration	Point estimate (95% CI)	*p* Values
Potential outcome	Normal	227.5 min (209.4, 245.5)	<.001
	High	188.5 min (162.0, 215.0)	<.001
Average treatment effect		−39.0 min (−68.6, −9.35)	.010

Note: The *p* values correspond to a test of the null hypothesis that the potential outcome or average treatment effect is equal to zero.
Abbreviation: CI, confidence interval.

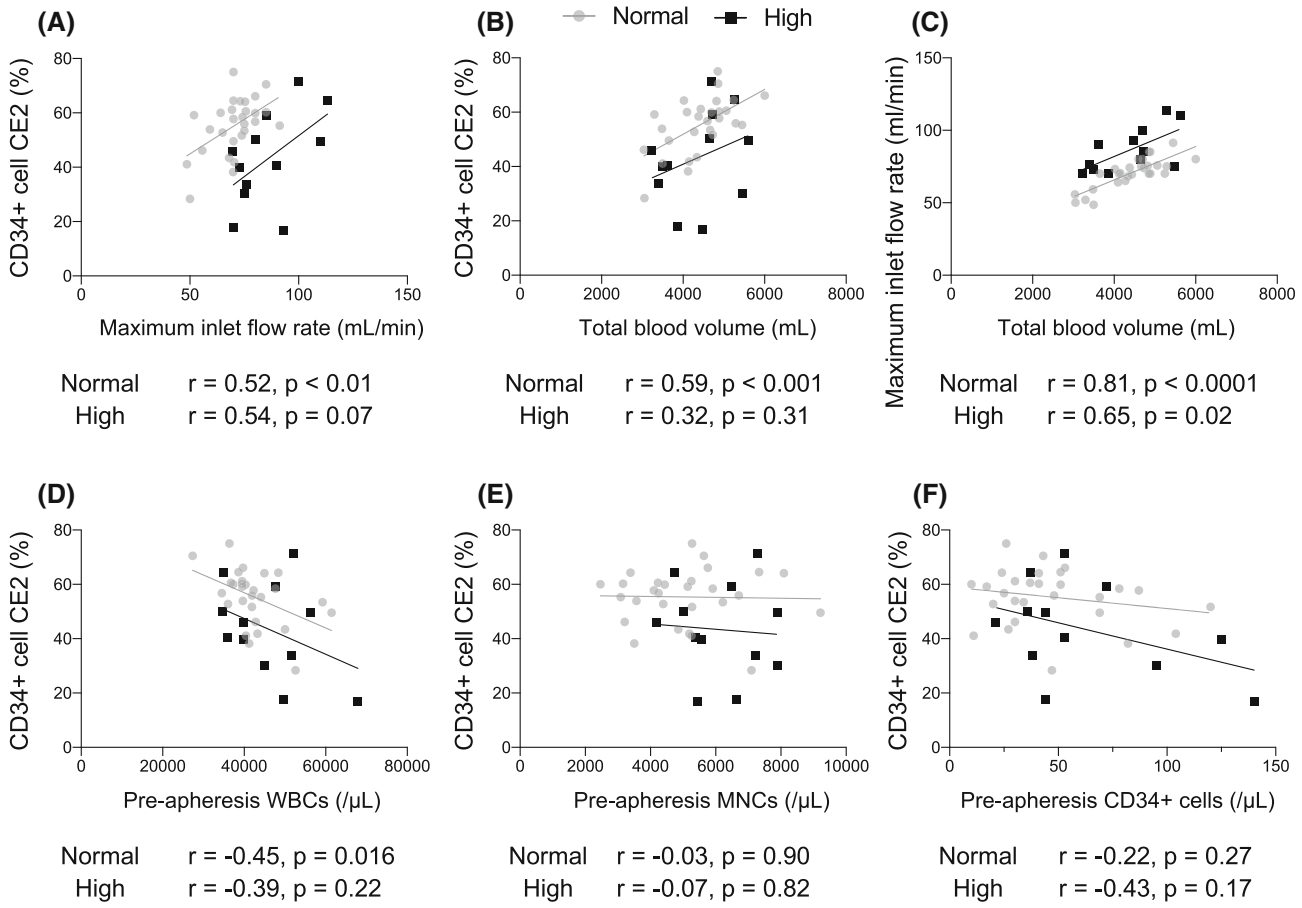

FIGURE 1 The correlations between the CD34+ cell CE2, maximum inlet flow rate, and total blood volume in allogeneic peripheral blood stem cell harvesting data. CE, collection efficacy; High, high sodium citrate concentration for the anticoagulant; MNC, mononuclear cell; Normal, normal sodium citrate concentration for the anticoagulant; WBC, white blood cell.

the use of heparin to change the AC ratio beyond the recommended range (6:1–15:1), to the best of our knowledge, this is the first report on the use of sodium citrate alone.

The processing time may partially depend on the venous access. In this study, the same indwelling cannula was used for peripheral venous access in allogeneic donors. The cannula has a pressure capacity of up to 209 mL/min; however, centrifugal component separators do not require high speeds for cell separation.[2] There were no cases where the inlet flow rate could not be increased for physical reasons related to venous access. Instead, the maximum inlet flow rate was dependent on the TBV as opposed to the venous access.

In this study, significant differences between the NSC and HSC groups were observed in the AC ratio, AC injection rate, and total amount of AC owing to changes in the AC composition during allogeneic PBSC apheresis. The changes in the AC composition did not occlude the extracorporeal circulatory circuit. In terms of safety, they did not increase citrate-related reactions, which are often a problem during apheresis, and did not worsen the platelet count or cause electrolyte abnormalities (e.g., ionized calcium, potassium, and magnesium) in blood tests. Moreover, the total CD34+ cell yield did not differ between the NSC and HSC groups. In addition, the volume of the collection bag was reduced in the HSC group. As the collection pump flow rate did not change in most apheresis cases, it is thought that the collection bag volume decreased owing to the shorter collection time.

Allogeneic PBSCs can be administered to patients on the same day or on the day after they are collected, or they can be frozen and administered later.[15] Reducing the volume of harvested products is likely to have the secondary benefit of simplifying the administration of live PBSCs and cell processing for cryopreservation following apheresis. However, in this study, the HSC group showed a decrease in the CD34+ cell CE2 (Table 1). Although there are differences in the procedure used to collect

CD34+ cells and MNCs (e.g., the machine and AC), previous studies have reported that high inlet flow rates reduce the CD34+ cell CE and MNC CE.[16,17] Regarding the decrease in CE, these studies have suggested that the target cells may not have had sufficient time to settle in the buffy coat because of the reduced dwell time in the centrifuge.[16,17] If the reasoning is correct, our results showing a positive correlation between the CD34+ cell CE2 and maximum inlet flow rate seem contradictory to the expected outcome (Figure 1A). However, one of the factors that determines the maximum inlet flow rate is the TBV, which depends on sex, height, and weight. Here, the maximum inlet flow rate was positively correlated with the TBV in both NSC and HSC groups (Figure 1C). Further, in the NSC group, the CD34+ cell CE2 showed a positive correlation with the TBV (Figure 1B). Therefore, the correlation between the CD34+ cell CE2 and maximum inlet flow rate may have been influenced by multiple factors.

In contrast, the CD34+ cell CE2 was negatively correlated with the pre-apheresis WBC count in the NSC group (Figure 1D). One study proposed that a larger number of cells may cause the collection chamber to fill faster, resulting in more time dedicated to flushing into the collection bag and more time when the chamber is not filled with the targeted cells.[16] Another study proposed that donors with a high number of WBCs and platelets might have a thick buffy coat, which prevents deep digging into the interface and filling of the collection chamber with target cells.[18] Although we used the continuous MNC protocol of Spectra Optia, which differs from the apheresis procedure for the chamber system, these possibilities may help explain why the CD34+ cell CE2 was lower in the HSC group than in the NSC group. The HSC group, with a large AC ratio, leading to low AC dilution, may have a higher WBC concentration than the NSC group. This seems to be consistent with the negative correlation between the pre-apheresis WBC count and CD34+ cell CE2.

Apheresis using HSC may be applied not only to the harvest of allogeneic PBSCs from donors, but also to the harvest of autologous PBSCs and CD3+ cells for tisagenlecleucel from patients. Furthermore, this method may be applied to pediatric cases. Apheresis in younger children is typically performed under anesthesia.[19] Complications occur more frequently during apheresis in children than in adults, and attention must be paid to citric-related reactions and lower blood pressure.[4] To reduce the burden on the patient, it is desirable to harvest the target cells in a short time period. If apheresis using HSC can be applied to children, the amount of AC solution to be administered will be reduced and apheresis will be possible in a shorter period, which is advantageous for children. In the future, we hope to accumulate more adult and pediatric cases of apheresis using allogeneic and autologous PBSCs and autologous CD3+ cells for tisagenlecleucel.

This study has some limitations. First, this study was limited to apheresis and did not investigate the clinical impact of the administered products on the recipients. Second, this was a retrospective study with a small, heterogeneous population and purely descriptive data. Therefore, larger prospective studies are required to confirm these findings. However, the reported results and the numerous steps performed will be beneficial for future studies aimed at improving leukocytapheresis methods.

In conclusion, to the best of our knowledge, our study is the first to perform apheresis by changing the citric acid concentration in the AC solution. This method allowed us to avoid large-volume infusions of the AC solution, increase the inlet flow rate to shorten the apheresis time, and reduce the product volume. Considering our findings, the use of a highly concentrated sodium citrate solution may reduce the burden on donors.

AUTHOR CONTRIBUTIONS

Masaya Abe: Investigation, visualization, writing—original draft. **Keiko Fujii**: Conceptualization, data curation, investigation, methodology, project administration, writing—original draft. **Toshiharu Mitsuhashi**: Formal analysis, validation. **Wataru Kitamura**: Investigation. **Kazuhiro Ikeuchi**: Investigation. **Takuya Fukumi**: Investigation. **Kana Washio**: Investigation. **Fumio Otsuka**: Supervision. **Yoshinobu Maeda**: Supervision. **Nobuharu Fujii**: Conceptualization, methodology, writing—review and editing.

ACKNOWLEDGMENTS

The authors would like to express their appreciation for the contributions of Naoe Takagi, Yachiyo Masuda, Ayumi Okada, and all the doctors and nurses at Okayama University Hospital. The authors would also like to thank Editage for the English language review.

CONFLICT OF INTEREST STATEMENT

The authors have disclosed no conflicts of interest.

ORCID

Keiko Fujii https://orcid.org/0009-0005-7614-2448
Wataru Kitamura https://orcid.org/0000-0002-8021-4732
Nobuharu Fujii https://orcid.org/0000-0002-8043-7768

REFERENCES

1. Ward DM. Conventional apheresis therapies: a review. J Clin Apher. 2011;26:230–8.
2. Lee G, Arepally GM. Anticoagulation techniques in apheresis: from heparin to citrate and beyond. J Clin Apher. 2012;27:117–25.
3. Mollison PL. The introduction of citrate as an anticoagulant for transfusion and of glucose as a red cell preservative. Br J Haematol. 2000;108:13–8.
4. Michon B, Moghrabi A, Winikoff R, Barrette S, Bernstein ML, Champagne J, et al. Complications of apheresis in children. Transfusion. 2007;47:1837–42.
5. Yuan S, Ziman A, Smeltzer B, Lu Q, Goldfinger D. Moderate and severe adverse events associated with apheresis donations: incidences and risk factors. Transfusion. 2010;50:478–86.
6. Hoad VC, Castren J, Norda R, Pink J. A donor safety evidence literature review of the short- and long-term effects of plasmapheresis. Vox Sang. 2023;119(2):94–101. https://doi.org/10.1111/vox.13512
7. Fujii K, Fujii N, Kondo T, Mitsuhashi T, Nakamura M, Seike K, et al. Effectiveness of supplemental oral calcium drink in preventing citrate-related adverse effects in peripheral blood progenitor cell collection. Transfus Apher Sci. 2021;60:103147.
8. Bolan CD, Yau YY, Cullis HC, Horwitz ME, Mackall CL, Barrett AJ, et al. Pediatric large-volume leukapheresis: a single institution experience with heparin versus citrate-based anticoagulant regimens. Transfusion. 2004;44:229–38.
9. Dettke M, Buchta C, Wiesinger H, Maas JH, Strate A, Chen Y. Anticoagulation in large-volume leukapheresis: comparison between citrate- versus heparin-based anticoagulation on safety and CD34 (+) cell collection efficiency. Cytotherapy. 2012;14:350–8.
10. Rajsp P, Branka M, Besson N, Tanzmann A, Worel N. Impact of mobilization strategies on peripheral blood stem cell collection efficiency and product quality: a retrospective single-center study. Cancers. 2022;14:6259.
11. Hobbs C, Green H, Fernandez R. The efficiency of a continuous versus an intermittent apheresis method for collection of hematopoietic progenitor stem cells: a systematic review. J Clin Apher. 2023;38:472–80.
12. Bolan CD, Greer SE, Cecco SA, Oblitas JM, Rehak NN, Leitman SF. Comprehensive analysis of citrate effects during plateletpheresis in normal donors. Transfusion. 2001;41:1165–71.
13. Abe M, Fujii K, Fujii N, Mitsuhashi T, Fukumi T, Sumii Y, et al. Oral calcium supplementation versus placebo in mitigating citrate reactions during apheresis: an open-label randomized control trial. Hematol Transfus Cell Ther. 2024;46(Suppl 6):S234–40.
14. Kondo T, Fujii K, Fujii N, Sumii Y, Urata T, Kimura M, et al. Efficient granulocyte collection method using high concentrations of medium molecular weight hydroxyethyl starch. Transfusion. 2023;63:1344–53.
15. Parody R, Caballero D, Marquez-Malaver FJ, Vazquez L, Saldana R, Madrigal MD, et al. To freeze or not to freeze peripheral blood stem cells prior to allogeneic transplantation from matched related donors. Eur J Haematol. 2013;91:448–55.
16. Burgstaler EA, Bryant SC, Winters JL. Comparison of hematopoietic progenitor cell collection using different inlet flow rates with the Fenwal Amicus. J Clin Apher. 2022;37:206–16.
17. Lin JS, Burgstaler EA, Pineda AA, Gertz MA. Effects of whole blood flow rates on mononuclear cell yields during peripheral blood stem cell collection using Fenwal CS 3000 plus. J Clin Apher. 1995;10:7–11.
18. Brauninger S, Bialleck H, Thorausch K, Seifried E, Bonig H. Mobilized allogeneic peripheral stem/progenitor cell apheresis with spectra Optia v.5.0, a novel, automatic interface-controlled apheresis system: results from the first feasibility trial. Vox Sang. 2011;101:237–46.
19. Pulsipher MA, Levine JE, Hayashi RJ, Chan KW, Anderson P, Duerst R, et al. Safety and efficacy of allogeneic PBSC collection in normal pediatric donors: the pediatric blood and marrow transplant consortium experience (PBMTC) 1996-2003. Bone Marrow Transplant. 2005;35:361–7.

How to cite this article: Abe M, Fujii K, Mitsuhashi T, Kitamura W, Ikeuchi K, Fukumi T, et al. Novel method of leukocytapheresis using a highly concentrated sodium citrate solution alternative to acid citrate dextrose solution A. Transfusion. 2025. https://doi.org/10.1111/trf.18280