Original Article

# Autologous peripheral blood stem cell harvest: Collection efficiency and factors affecting it

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**Abstract:**

**Background:** Harvest of hematopoietic progenitor cells via leukapheresis is being used increasingly for transplants in India. Adequate yield of cells per kilogram body weight of recipient is required for successful engraftment. Collection efficiency (CE) is an objective quality parameter used to assess the quality of leukapheresis program. In this study, we calculated the CE of the ComTec cell separator (Fresenius Kabi, Germany) using two different formulae (CE1 and CE2) and analyzed various patient and procedural factors, which may affect it. **Materials and Methods:** One hundred and one consecutive procedures in 77 autologous donors carried out over 3 years period were retrospectively reviewed. Various characteristics like gender, age, weight, disease status, hematocrit, preprocedure total leukocyte count, preprocedure CD34 positive (CD34+) cells count, preprocedure absolute CD34+ cell count and processed apheresis volume effect on CE were compared. CE for each procedure was calculated using two different formulae, and results were compared using statistical correlation and regression analysis. **Results:** The mean CE1 and CE2 was 41.2 and 49.1, respectively. CE2 appeared to be more accurate indicator of overall CE as it considered the impact of continued mobilization of stem cells during apheresis procedure, itself. Of all the factors affecting CE, preprocedure absolute CD34+ was the only independent factor affecting CE. **Conclusion:** The only factor affecting CE was preprocedure absolute CD34+ cells. Though the mean CE2 was higher than CE1, it was not statistically significant.

**Key words:**

Collection efficiency, leukapheresis, peripheral blood stem cells

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## Introduction

Harvest and transplantation of hematopoietic progenitor cells is used increasingly in the treatment of several blood disorders, malignancies, and genetic abnormalities.[1-3] Progenitor stem cells are rare and found primarily in the bone marrow, with extremely low frequencies (0.01-0.5% of nucleated cells) in peripheral blood.[4] However, mobilization of cells into the peripheral blood using growth factors and/or chemotherapy results in increased numbers of circulating peripheral blood stem cells (PBSCs), facilitating harvest from peripheral blood.[5,6] These stem cells are collected by leukapheresis and quantified in terms of CD34 positive (CD34+) cells.

The adequacy of a collection is measured by the number of CD34+ cells per kilogram of recipient body weight. Successful engraftment has been observed with counts ranging from 2 to 5 × $10^6$ CD34+ cells/kg.[7,8] A minimum threshold of 10-30 circulating CD34+ cells per microliter affords such satisfactory yields.[9-11] These levels of circulating cells are achieved between 5 days and 7 days after initiating mobilization with growth factors[12,13] and this is considered an appropriate time to initiate harvest. Usually, two to four blood volumes are processed per leukapheresis procedure, in spite of which sometimes serial collections may be necessary to attain the appropriate CD34+ cell dose for transplantation.[9-11]

The success of PBSC transplantation mainly depends on the transfusion of sufficient CD34+ cell dose to reconstitute patients' hematopoiesis rapidly.[14] This can be gauged primarily by patient outcome measures like engraftment, transplant-related morbidity or mortality. Apart from the outcome, collection efficiency (CE) is one of the objective quality parameters which can be used



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to assess a cell separator's potential for generating high yields of extracted cells and hence facilitating successful transplants. However, data on the CE of cell separators is limited, especially with reference to CD34+ cell collection.[15]

Even though technical advances such as improved automated cell separators capable of efficient collections have facilitated the increased application of PBSC transplantation in India, we did not encounter any published report investigating CE. Hence, in this study, we analyzed various aspects of the CE of 101 consecutive leukapheresis procedures.

## Materials and Methods

One hundred and one consecutive leukapheresis procedures in 77 autologous donors carried out in the Department of Transfusion Medicine at a tertiary care hospital in the National Capital Region of India between August 2010 and December 2013 were reviewed retrospectively. Collections were carried out in only autologous donors. Informed consent was obtained from each autologous donor prior to collection. The disease indications for which collections were carried out are summarized in Table 1.

Table 1

### *Study design*

There was a retrospective comparison of two different methods used to calculate CE and analysis of various donor and procedural factors, which may affect CE. Various parameters which contribute toward prediction and attainment of CD34+ cell yield are enumerated in Table 2.

### *Mobilization regimen and time of harvest*

Autologous donors underwent mobilization with hematopoietic granulocyte colony-stimulating factor (G-CSF: Neupogen, Amgen, München, Germany) with 10 μg/kg divided into two doses, administered sub-cutaneously. Cells were harvested on the 5$^{th}$ day of mobilization.

**Table 1: Disease-wise distribution of PBSC donors**

| Diagnosis | Number of patients |
|---|---|
| Multiple myeloma | 64 |
| Hodgkin's disease | 7 |
| NonHodgkin's lymphoma | 3 |
| Germ-cell tumor | 2 |
| Amyloidosis | 1 |
| Total | 77 |

PBSC: Peripheral blood stem cell

### *CD34 positive cell count determination*

CD34 positive cell counts were determined preprocedurally in the autologous donor's peripheral blood, and in the leukapheresis product, by flow cytometry (FACS Calibur, Becton Dickinson, Heidelberg, Germany). In 48 cases, enumeration was also done in the peripheral blood 1-h after the leukapheresis procedure. Flow cytometric analysis followed the accepted protocol given by the International Society of Hematology and Graft Engineering.[16] The total leucocyte count (TLC) was done in calibrated automated cell counter (Sysmex XE 2100; Sysmex Corporation, Japan) and monoclonal CD34 antibody (clone 8G12; BD Biosciences, San Jose, US) and CD45 (clone 2D1; BD Biosciences, San Jose, USA) were used.

### *Leukapheresis procedures*

All procedures were carried out using the Fresenius ComTec cell separator (Fresenius Kabi, Bad Homburg, Germany). The machine was calibrated and worked on its default settings. The P1YA kit was used, and the collection program was set to mononuclear cells (autoMNC) software version 4.03.07 (Fresenius Kabi, Bad Homburg, Germany). The autoMNC program is an established program that has been shown to result in higher CE and better prediction of the CD34+ yield.[17,18]

The number of cycles and thereby the volume of blood processed were adjusted in such a manner that the desired yield was set at a mean value of $4 \times 10^6$ cells/kg. These settings resulted in large volume leukapheresis in all cases, with a mean Acid-Citrate-Dextrose (ACD): Blood ratio of 1:15. The extra-corporeal volume was low (around 170 ml) which patients/autologous donors tolerated well and none required additional fluids or blood component transfusion during the procedure. The vitals were monitored hourly and remained stable in all the autologous donors (patient-donors). The autologous donors were administered prophylactic oral calcium (tablet shelcal 500 mg) every 30 min during the procedure.

### *Collection efficiency*

Collection efficiency, a percentage measure of the cell separator's ability to extract maximum number of CD34+ cells from the cells available in the donor's blood was calculated as follows[15-19]:

$$CE1 = \frac{\text{Leukapheresis product CD34 (\%)} \times \text{TLC} \times \text{volume of product}}{\text{Preprocedural peripheral blood CD34 (\%)} \times \text{TLC} \times (\text{total blood volume processed-ACD})}$$

**Table 2: Leukapheresis characteristics of PBSC donors**

| Parameters | Mean ± SD | Median | Range |
|---|---|---|---|
| Age (years) | 45.24±16.1 | 53 | 5-66 |
| Weight (kg) | 67.56±18.1 | 71 | 20-105 |
| Hematocrit (%) | 32.8±5.1 | 33.6 | 19-42 |
| Preprocedural TLC ($\times 10^3/\mu L$) | 36.26±17.5 | 35.9 | 1-90 |
| Preprocedural CD34+ count ($\times 10^3/\mu L$) | 0.14±0.15 | 0.1 | 0.01-1.25 |
| Processed blood volume (μL) | 18338.76±8965 | 16,223 | 4388-44,984 |
| Product TLC ($\times 10^3/\mu L$) | 190.44±90.6 | 185.19 | 14-401 |
| Product CD34+ count ($\times 10^3/\mu L$) | 0.39±0.7 | 0.22 | 0.05-5.7 |
| Yield ($\times 10^6$ cells/kg) | 3.6±3.0 | 2.8 | 0.38-18.25 |
| CE1 (%) | 41.2±28.7 | 36.8 | 7.40-171.4 |
| CE2 (%) | 49.1±30.8 | 24.7 | 8.14-179.75 |

CE: Collection efficiency, PBSC: Peripheral blood stem cell, TLC: Total leukocyte count, SD: Standard deviation

In addition, an alternate formula, which factored in the postprocedural peripheral blood CD34+ cell count was used to calculate CE in 48 autologous cases.[18-20]

$$CE2 = \frac{\text{Leukapheresis product CD34 (\%)} \times \text{TLC} \times \text{volume of product}}{\text{(Average of pre and postprocedural peripheral blood CD34+ cell count) (\%)} \times \text{TLC} \times \text{(total blood volume processed-ACD)}}$$

### *Statistical methods*

All statistical analysis was carried out using software Microsoft Excel (Microsoft Corporation, Washington, USA) and SPSS (SPSS, Chicago, USA). CE1 and CE2 were compared for 48 cases where data was available. In these 48 cases paired *t*-test was also applied to compare preprocedure average CD34+ counts and postprocedure CD34+ counts. In cases where more than one procedure was carried out on the same donor, various characteristics of the collection on the first and subsequent days were compared. Linear regression analysis was performed to evaluate the impact of donor age, weight, hematocrit, preprocedure TLC, preprocedure CD34+ cell count, absolute preprocedure CD34+ cell count and processed apheresis volume on CE.

## Results

**Table 2**

### *Characteristics of collection efficiency*

The mean CE calculated using the formula CE1 was 41.2% in autologous donors (range 7.40-171.49%).

In the 48 cases where CE2 was also calculated, the mean CE2 was 49.1% (range 8.14-179.75%). It was observed that the CE2 value in almost every case was higher than the corresponding value of CE1.

Both leukocytes and CD34+ cells were concentrated in the product many times their initial number in the peripheral blood. Leukocytes showed an overall average five-fold (range 1.6-33.64) increase in number. CD34+ cells were concentrated 11-fold on an average (range 3.1-90.05).

### *Inter-day collection efficiency*

Twenty-four donors underwent repeat procedures to collect an adequate yield. Various parameters as on the 1st and 2nd collection day were compared in these serial collections. It was found that CE was not affected by the day of collection.

However, the hematocrit was significantly lower on the second day as compared to the first (mean 29.4% vs. 32.3%) while preprocedural TLC increased significantly on the second day when compared with the first (33.59 vs. 26.65 × $10^3$ cells/μL) at $P < 0.01$.

### *Factors affecting collection efficiency*

Out of all the factors analyzed by linear regression analysis, only preprocedural absolute CD34+ cell count showed a significant ($P = 0.003$) relationship with CE1 [Table 3]. The preprocedural CD34+ cell count was also found to be strongly correlated with both postprocedural CD34+ cell count in the product ($r = 0.83$) and the yield (per kilogram recipient body weight) ($r = 0.34$).

## Discussion

The CD34+ cell yields obtained through leukapheresis are partly determined by the efficiency of collection, making CE an important parameter for successful harvests. CE values are highly variable, as seen in the literature,[17,18,20-29] with mid-values as low as 30%[25] and as high as 85%.[23] Apart from donor characteristics, the type of collection device, cell separation mechanism, program and operator settings all contribute towards this variability.[17,18,26,30,31]

The CE1 in the present study ranged from 7.40% to 171.49% in autologous donations. The values above 100% may be explained by the intra-collection mobilization phenomenon, which caused fluctuation of peripheral CD34+ cell concentration by recruiting additional cells from the bone marrow during the leukapheresis procedure.[15,32,33]

The mean CE1 of 41.2 in the present study was slightly lower than the values in many other studies, including those done on the same cell separator.[17,18,20] This may be due to differences in operation, as well as the fact that the average leukapheresis volumes at authors' institute were higher than the blood volumes processed at most other centers. Larger volumes were processed in an attempt to harvest an adequate dose in a single procedure to minimize expense and patient discomfort, even at the cost of a lower CE.

Out of the two formulae used to calculate CE, CE2 would possibly be more accurate indicator of efficiency since it also considers a decrease in CD34+ cells in the patient. CE2 shows consistently higher values than CE1 in almost all cases where both were calculated ($n = 48$). This is because the impact of fluctuation in the CD34+ concentration, due to intra-procedural mobilization or dilution of the blood by anti-coagulant, is accounted for in CE2 by taking the average of both pre and postprocedural CD34+ cell counts. Calculations with CE1, which only factors in the preprocedural

**Table 3: Results of regression analysis performed on factors affecting CE**

| Model | Unstandardized coefficients | | Standardized coefficients | *t* | Significance |
|---|---|---|---|---|---|
| | B | SE | Beta | | |
| Constant | 22.273 | 17.648 | | 1.262 | 0.210 |
| Age | 0.093 | 0.164 | 0.052 | 0.569 | 0.571 |
| Weight | −0.056 | 0.224 | −0.035 | −0.248 | 0.805 |
| Preprocedure hematocrit (%) | −0.009 | 0.084 | −0.010 | −0.106 | 0.916 |
| Preprocedure TLC (×$10^3$/μL) | −0.009 | 0.182 | −0.005 | −0.047 | 0.963 |
| Preprocedure CD34 (%) | −13.993 | 17.674 | −0.318 | −0.792 | 0.431 |
| Preprocedure absolute CD34 ($10^3$/μL) | 264.751 | 87.845 | 1.231 | 3.014 | 0.003 |
| Volume processed | 0.001 | 0.001 | 0.274 | 1.300 | 0.197 |

CE: Collection efficiency, TLC: Total leukocyte count, SE: Standard error

CD34+ cell count, reflect a conservative estimate of the true CE of the cell separator since CD34+ counts usually drop during leukapheresis. The preprocedure average donor CD34+ counts of 0.07 was significantly higher than the postprocedure donor CD34+ counts of 0.05 ($n = 48$; $P = 0.007$). This was reaffirmed in the present study with the mean CE2 being 49.1 as compared to CE1 which was 41.2. Other than the difference in the mean value, the CE2 value was higher than the corresponding value of CE1in almost all 48 cases.

The CE of the cell separator is also reflected in its power to extract and concentrate the cells of interest. Matic *et al.*,[34] observed that CD34+ cells were enriched 38-fold in the apheresis product when less than one total blood volume was processed, but the efficiency decreased as higher volumes were processed. In collections with a TLC <5,000 cells/μL, the concentration averaged 50-fold, while in cases where TLC lay between 45,000 and 50,000 cells/μL, the final CD34+ concentration averaged eight times the number in the peripheral blood.[34] In this study, 4.1 blood volumes were processed on an average, and per procedural TLC was much higher than 5000 cells/μL, which resulted in an average 11-fold concentration in the number of CD34+ cells, which falls within the range of values observed by Matic *et al.*[34]

Although multiple collections can be carried out on donors who do not reach the target yield within one procedure, this may be prohibitive due to poor clinical condition of the patient, decrease in CD34+ cell number and cost of additional procedures.[35] Hence attempts should be made to minimize the number of leukapheresis procedures. In the present study, only 24 donors necessitated a second (or more) collection. The lowered hematocrit seen on the 2nd day was to be expected, as leukapheresis also results in some red cell loss.[25] The increase in TLC can be attributed to the continued effect of G-CSF resulting in recruitment of cells from the bone marrow into the bloodstream. However, this had no effect on the CE, which did not differ significantly on different days of collection, similar to the finding of Ford *et al.*[15]

Optimization of CD34+ cell CE requires the identification of factors impacting this parameter. Although various studies have been conducted, no factor has yet been identified which uniformly and individually predicts CE. Multiple regression analysis carried out in the present study to evaluate the impact of age, weight, disease status, hematocrit, preprocedure TLC, preprocedure CD34+ cell count, preprocedure absolute CD34+ cell count and processed apheresis volume identified preprocedure absolute CD34+ cell number as the sole significant predictor for CE. Sarkodee-Adoo *et al.*, also found that circulating CD34+ count had a modest effect on CE, although in their case an inverse correlation was seen.[36] Both these results are further at odds with the findings of Ford *et al.*, who stated that peripheral CD34+ count is not associated with CE.[15] This underlines the fact that the jury is still out on the relationship between CD34+ cells and CE and possibly a larger study would finally establish an association-none, directly proportional or indirectly proportional.

Total leucocyte count has been found to be an important independent factor which inversely affects CE in some studies,[15,29,34] whereas in others it did not show significant correlation with CE,[36] similar to the present results. Similarly, the role of hematocrit has also been controversial. While Mehta *et al.*, and Sarkodee-Adoo *et al.*, suggest that there is no correlation between hematocrit and CE[25,36] a finding echoed in the present study as well as in the findings of Ford *et al.*, which shows an inverse correlation between the two parameters.[15] Similarly, age is not a significant factor in the present study, a finding supported by Ford *et al.*,[15] but at odds with the results of Ikeda *et al.*[31] No association was found between weight and CE.[15,36] Factors which did not show an association with CE in the present results but are recorded elsewhere as being significant include disease status[3,15] and apheresis volume.[36]

Apart from these factors (CD34+ count/TLC/hematocrit/age/weight/disease status/apheresis volume) many other factors have also been studied with variable results, including gender,[15,36] chemotherapy regimen and number of cycles,[15] disease invasion of the bone marrow,[15,31] mobilization regimen and rate[15,31,36] albumin[15] platelets[36] etc. Additionally, the relative impact of each of these factors is difficult to calculate for any one procedure. Thus, variation in CE is undoubtedly complex and multi-factorial.[15]

Though studies have also shown a correlation between preprocedural circulating CD34+ cell counts and the number of cells in the apheresis product[8-11,25,29,35] and the final yield/kg of CD34+ cells.[14,19,37,38] The present study shows that peripheral CD34+ cell counts are better predictors of yield than CE especially, when the CD34+ counts are higher. However, CE is helpful in determining yield where the peripheral CD34+ counts are low.

## Conclusion

Collection efficiency is an important quality control parameter to monitor the autologous and allogenic harvests, especially in donors where the CD 34+ counts are low. However, CE is affected by a wide range of procedural factors and donor characteristics and shows a lot of variability in the clinical setting. Not only does the average CE value vary considerably among different centers, there is also no consensus on which factors impact CE and its variability. In the present study, the average CE was 41.2% and preprocedural absolute CD34+ cell count was the only significant predictor for CE.

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### Conflicts of interest

There are no conflicts of interest.

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