ORIGINAL RESEARCH

Comparative analysis of neutrophil engraftment following mobilisation with G-CSF vs G-CSF plus plerixafor after peripheral blood haematopoietic stem cell transplant

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ABSTRACT

Introduction: Haematopoietic stem cell transplantation (HSCT), also known as bone marrow transplantation (BMT), is being increasingly used for pathologies such as like leukaemia, lymphoma, and multiple myeloma, as well as other haematological abnormalities. Risks include infection, graft-versus-host disease, and graft failure. The stem cells are collected using apheresis and stored for transplantation. Mobilizing agents like cytokines, chemokines, and small molecules help release stem cells into the blood. Poor mobilization can lead to complications. The decision to undergo HSCT depends on the patient's condition and healthcare team's advice. We undertook this study to find out the efficacy of G-CSF alone versus a combination of G-CSF and Plerixafor (administered 6-8 hours before harvesting) in poorly mobilizing CD34+ individuals. **Materials and methods:** It was an observational study, data was collected from two transfusion medicine department (Medical College , Department of IHBT and NSH, Howrah, Department of Transfusion medicine) and retrospectively analysed using DATAtab online software. informed consent was obtained from the participants. A total thirty-six autologous and ten 6/6 HLA matched sibling allogenic peripheral blood haematopoietic stem cell (PBSCs) transplant recipients (aged 5- 60 years) were analysed from records during the period of 2016 to 2023. All of them were haemato-oncological patients and refractory to chemotherapeutic agents or not responding to conventional treatment. Efficacy of G-CSF alone versus a combination of G-CSF and Plerixafor (administered 6-8 hours before harvesting) in poorly mobilizing CD34+ individuals. The observed values for engraftment as absolute neutrophil count (ANC) in both the groups were compared by using different statistical parameters in DATAtab software. 'p' $\leq$ 0.05 value was considered as significant.**Results:**N group was found to have higher values for the dependent variable neutrophil engraftment (Mdn = 11) than the Y group represent G-CSF used CD34+ mobilisation along with single dose plerixafor (Mdn = 10). The difference between N and Y with respect to the dependent variable neutrophil engraftment (ANC$\geq$500µl) was statistically significant, U=104.5, p=.018, r= 0.38. 0 group (without cryopreservation) has higher values for the dependent variable neutrophil engraftment (N) (M = 11.57, SD = 2.36) than the 1 group (with cryopreservation) (M = 11.23, SD = 2.39). The results of the descriptive statistics show that the autologous PBSC transplant group has lower values for the dependent variable absolute neutrophil engraftment (M = 10.45, SD = 0.83) than the allogenic PBSC transplant group (M = 15.22, SD = 2.44). the difference between auto and allogenic with respect to the dependent variable was statistically

significant, t(8.51) = -5.78, p = <.001, 95% confidence interval [-6.65, -2.88]. **Conclusion:** G-CSF plus plerixafor mediates faster engraftment as compared to Single dose G-CSF and the difference is found to be statistically significant.
Keywords: Plerixafor, G-CSF, Bone marrow transplantation, leukaemia.

INTRODUCTION

Haematopoietic stem cell transplantation (HSCT), also known as bone marrow transplantation (BMT), is a procedure used to treat various types of blood cancers, such as leukaemia, lymphoma, and multiple myeloma, as well as other blood disorders [1]. It involves the infusion of harvested haematopoietic stem cells to replace the damage or diseased bone marrow.

Haematopoietic stem cells are undifferentiated cells that could differentiated into various types of matured blood cells, such as red blood cells, white blood cells, and platelets [2]. These stem cells can be obtained from the bone marrow, peripheral blood, or umbilical cord blood.

The harvesting procedure by apheresis technique helps to collect haematopoietic stem cells from the matched sibling or unrelated donor or even the patient himself in certain cases. The stem cells are then processed and stored for future transplantation. The patients are monitored closely for potential complication, such as infection, graft-versus-host disease (GVHD), post-transplant graft failure, veno-occlusive disease (VOD), side-effects of immunosuppressive medications used to prevent GVHD [3].

Bone marrow transplant can a be potentially curative treatment for haematological and non-haematological malignancy and non-malignant haematological disorders, [4]. Haematopoietic stem cell transplantation (HSCT) has been shown increase complete remission and overall survival in transplant patients. Adequate number of peripheral blood haematopoietic stem cells are essential for successful engraftment. There are several different chemotherapeutic agents that are used for mobilisation of haematopoietic stem cells (HSC) from bone marrow niche into the peripheral blood. Mobilizing agents are:

1. Cytokines: Cytokines are proteins that regulate the behaviour of other cells. Some cytokines, such as granulocyte colony stimulating factor (G-CSF) and stem cell factor (SCF), can stimulate the release of HSCs from the bone marrow [5].
2. Chemokines: chemokines are small proteins that regulate the migration of cells. Some chemokines, such as stromal cell-derived factor-1 (SDF-1), can stimulate the migration of HSCs from the bone marrow into the peripheral blood [6].
3. Small molecules: Some small molecules, such as plerixafor, can also stimulate the release of HSCs from the bone marrow [7].

Poor mobilization of haematopoietic stem cells (HSCs) can have several negative effects, including a) reduced availability of HSCs for transplant, b) increased risk of infection, c) increased risk of bleeding and post-transplant transfusion requirement d) graft failure along with increase in hospital stay [8]. Haematopoietic stem cell transplant is a complex procedure with risks and potential complications, and suitability of HSCT depends on various factors, including the patient's age, overall health, and disease characteristics and peripheral mobilisation of CD34 cells from bone marrow periphery. The decision to undergo HSCT is made in collaboration between the patient their healthcare team, and a transplant specialist.

The mobilization of peripheral blood CD34+ cells is crucial for successful hematopoietic stem cell transplantation. We undertook this study to find out the efficacy of G-CSF alone versus a combination of G-CSF and Plerixafor (administered 6-8 hours before harvesting) in poorly mobilizing CD34+ individuals to attain post-transplant stabilization of Absolute Neutrophil Count (ANC) ≥ 500/µl. Additionally we also analysed correlation between the engraftment of ANC ≥ 500/µl and the ABO blood group system in both allogeneic and autologous transplant settings, the impact of cryopreservation on neutrophil engraftment, specifically achieving ANC ≥ 500/µl, is another area of interest, with variations between cryopreserved and non-cryopreserved units and a comparison of ANC counts of ≥ 500/µl in autologous versus allogeneic settings highlights differences in engraftment efficiency and outcomes in these two transplant modalities.

MATERIALS AND METHODS

Study subject

A total thirty-six autologous and ten 6/6 HLA matched sibling allogenic peripheral blood haematopoietic stem cell (PBSCs) transplant recipients (aged 5- 60 years) were analysed from records during the period of 2016 to 2023. All of them were haemato-oncological patients and refractory to chemotherapeutic agents or not responding to conventional treatment.

Study design

Both male and female haemato- oncological patients aged 5 to 60 years were included in the present study. The patients to whom the PBSC could not transfused due to death and patients with HLA a mismatch allele (6/6) was excluded from the present study. In the present study days of neutrophil engraftment were distributed in two arms. One group comprised the single agents for peripheral haematopoietic stem cell (CD34 cells) mobilising agents (G-CSF) and other

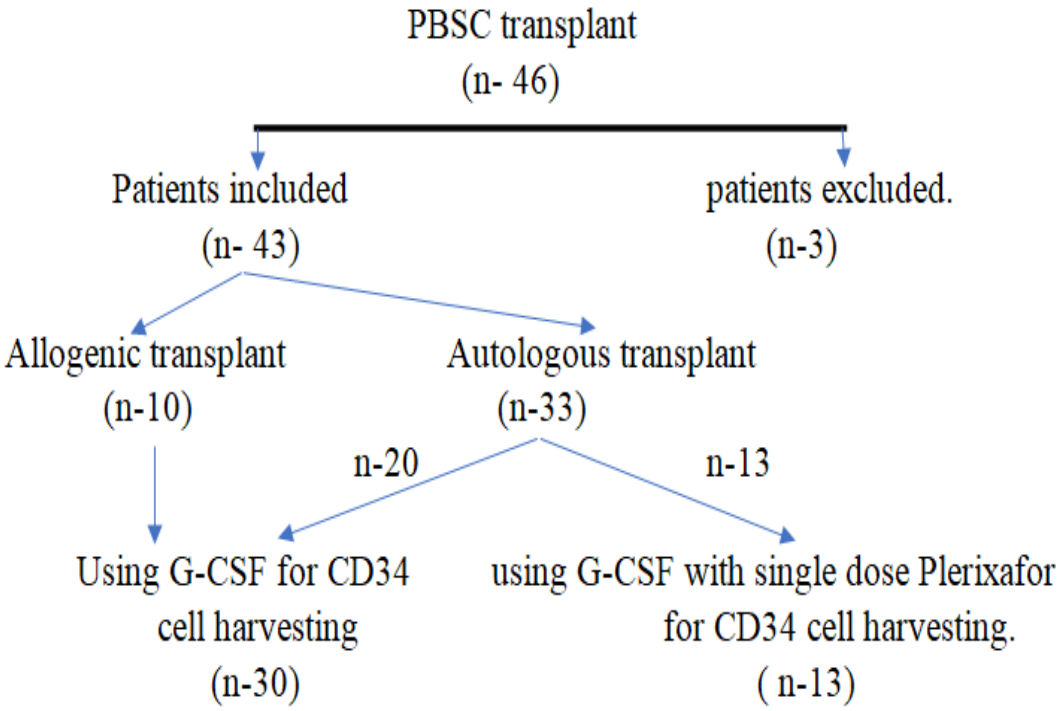
group comprised poor mobilisation with single agents, they were used additional single dose of plerixafor along with G-CSF. A written informed consent was obtained from everyone prior to PBSC transplantation.

Process of peripheral marrow stem cell mobilisation

The process of mobilisation of peripheral blood haematopoietic stem cell harvesting (PBSC) for apheresis involves several steps.

Growth factor administration (G-CSF): The patients were given a growth factor (G-CSF) 10 µg/kg/day in two divided doses for consecutive 5 days (day -4 to day 0) to facilitate the release of PBHSC from the bone marrow niche into the peripheral blood. Quantification of CD34 was done from the peripheral blood sample on 4th day of G-CSF injection. Sample was analysed for CD34+ count at nearest accredited centre, Kolkata by using panel BD system Cell plus 7AAD. Patients were selected for apheresis if the CD34 plus viable count ≥ 20 cells/ µl and viable CD34 and CD 45% ≥ 0.08%. [9]

Plerixafor administration: When the peripheral mobilization was poor that is viable CD34 plus viable count < 30 cells/ µl (range 1.13 to 22.80 cells/µl) and viable CD34 and CD 45% < 0.08% (range 0.03 to 0.07 %) [10] by a single chemical agent (not fulfil the above-mentioned quantification criteria), then dual agent G-CSF with single dose plerixafor 0.24 mg/kg not exceeding 40 mg/ day of body weight given prior to 6 to 8 hours of harvesting. Flow chart of peripheral blood haematopoietic stem cells given below (Figure-1).



Flowchart of figure 1 shows details of participants in the present study

Peripheral blood haematopoietic stem cell harvesting

After the desirable (2-5X10^6/kg) peripheral blood stem cell (CD34 cells) quantification, patient was shifted to apheresis room for harvesting of HSC cells in an aseptic condition [11]. Spectra Optia , Terumo BTS apheresis machine was used for CD34 collection. The apheresis procedure itself takes several hours (3-6 hours) and 6 patients experienced mild to moderate apheresis related complications during the procedure and was managed accordingly. A mid harvest (nearly 80-100 ml) was sent to accredited diagnostic laboratory nearer to Kolkata for calculating the required dose for an individual. In the present study doses was calculated for CD34 cells 2-5 X 10^6/ kg of recipients for transfusion. After collection of PBSCs, product dose in reference to yield was labelled and stored at dedicated blood bank refrigerator (4±2°C) in aseptic environment. Cryopreserved products also stored at -80°C with maintaining all documents of preservation. All cryopreserved PBSCs were thawed before transfusion and checked for $CD34^+$count and sterility testing.

Transportation of PBSC product bag from storage to bed side

All PBSCs product were transferred from storage facility to bone marrow transplant room by maintain a cold chain using ice liner.

Preparation of patients prior to transplantation
Number of cases undergone myeloablative and non-myeloablative regimen (agent used with dose and radiation) as per the standard disease specific protocol.

Procedure of transplantation
Product of PBSCs were infused to the recipients through central line on day + 1. Monitoring of transfusion reactions and recording vital parameters are meticulously done. After transfusion of PBSCs remaining content of the bag send for both bacterial and fungal culture.

Parameter studied during follow-up day +1 to discharge of the patients.
Post transfusion follow-up was monitored with specified interval-

- Daily: CBC, serum Na^{2+}, K^{+}, Mg^{2+}, Ca^{2+}, and glycaemic monitoring for diabetic patients.
- Alternate day: LFT, serum creatinine, LDH
- Weekly: anti A, anti B titter, DCT for allogenic patients.
- Monthly: RBC antigen chimerism

Post transplant irradiated PRBC and SDP supports.
Indication of PRBC transfusion: cutoff Hb level ≤8 gm/L

Prophylactic SDP transfusion:
Indication of prophylactic transfusion ≤ 10,000 without bleeding and irrespective of any active bleeding ≤ 20,000 count.

Analysis of results
The observed values for engraftment as absolute neutrophil count (ANC) in both the groups were compared by using different statistical parameters in DATAtab software. 'p' ≤ 0.05 value was considered as significant.Patients' follow-up parameter was noted to engraftment and data were compared as both arm by using online statistical software DATAtab, and p value was calculated.

RESULTS
The results of the descriptive statistics show that the N group represent G-CSF used for VD34+ mobilisation, higher values for the dependent variable neutrophil engraftment (Mdn = 11) than the Y group represent G-CSF used CD34+ mobilisation along with single dose plerixafor (Mdn = 10). Table shows descriptive statistics of patients using single mobilisation (only G-CSF) versus G-CSF with single dose plerixafor administration for CD34+ mobilisation during harvesting of PBSC collection followed by days of neutrophil engraftment after PBSCs transplantation. (Table- 1).

Table 1: Comparison of groups on the basis of dependent variable neutrophil engraftment values.

		n	Mean	Median	Standard deviation
N engf	N	30	12	11	2.6
	Y	13	10.23	10	0.73

Analysis of N group representing number of persons using G-CSF for CD34+ mobilisation and Y group represents G-CSF along with single dose Plerixafor used in poorly mobilised CD34+ for PBSC transplant is shown below (Table 2)

Table-2 Mann-Whitney U test for calculation of mean rank and sum rank of two groups

	n	Mean Rank	Sum of Ranks
N	30	25.02	750.5
Y	13	15.04	195.5
Total	43		

Comparative analysis of two arm showed p value 0.018 which was significant.

Table 3 shows Comparative analysis of two arm shows p value 0.018 which is significant at p = 0.05

	U	z	asymptotic p	exact p
N engf	104.5	-2.52	.012	.018

Days of neutrophil engraftment in N group (G-CSF only) and Y group (G-CSF with Plerixafor) was compared (Figure 2).

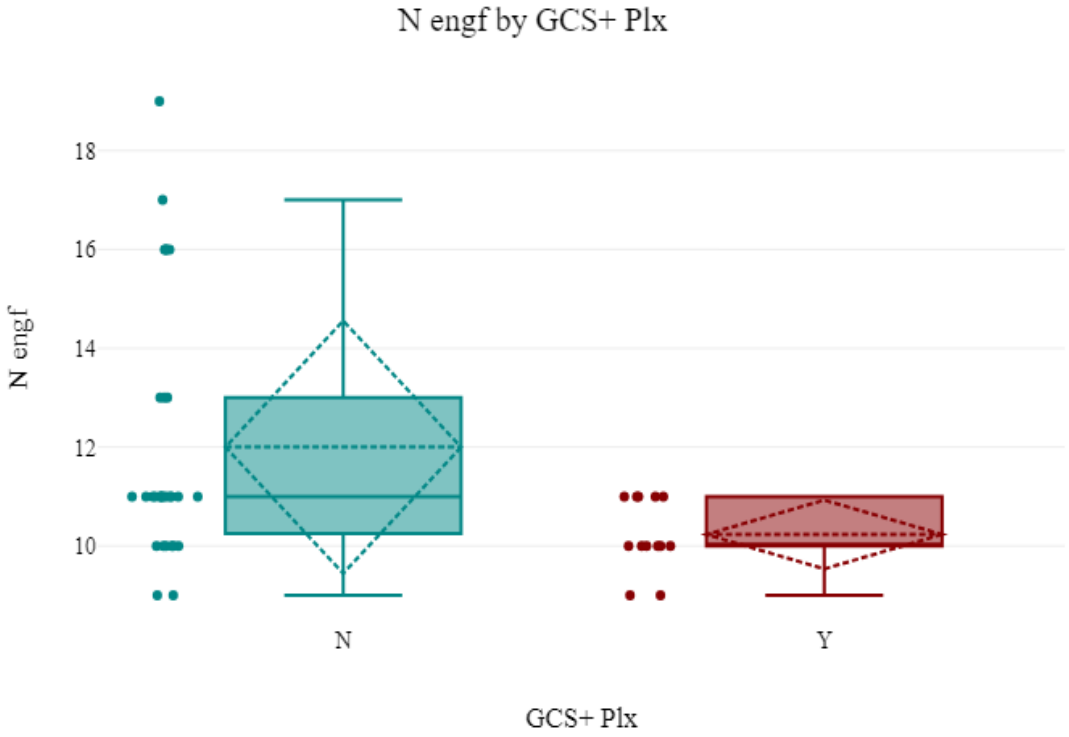


Figure-2 neutrophil engraftment in between two groups

A one-factor analysis of variance has shown that there was no significant difference between the categorical variable Bl.gr and the variable N engf $F = 0.38$, $p = 0.765$ Thus, with the available data, the null hypothesis is not rejected.

Effect size

η^2	η_p^2	Cohen's f^2
0.03	0.03	0.03
f	Classification according to Cohen (1988)	
0.2	weak effect	
0.15	moderate effect	
0.35	strong effect	

The ANOVA showed that there was no significant difference, so it is not reasonably possible to compute a post hoc test. Table -4, Figure-3

Table -4 descriptive statistics related to ANC in different blood groups.

		Frequency	Mean	Std. Deviation	Minimum	Maximum
N engf	O	16	11.53	3	9	19
	B	13	11.69	2.06	10	16
	A	8	11.63	2	10	16
	AB	6	10.4	0.55	10	11

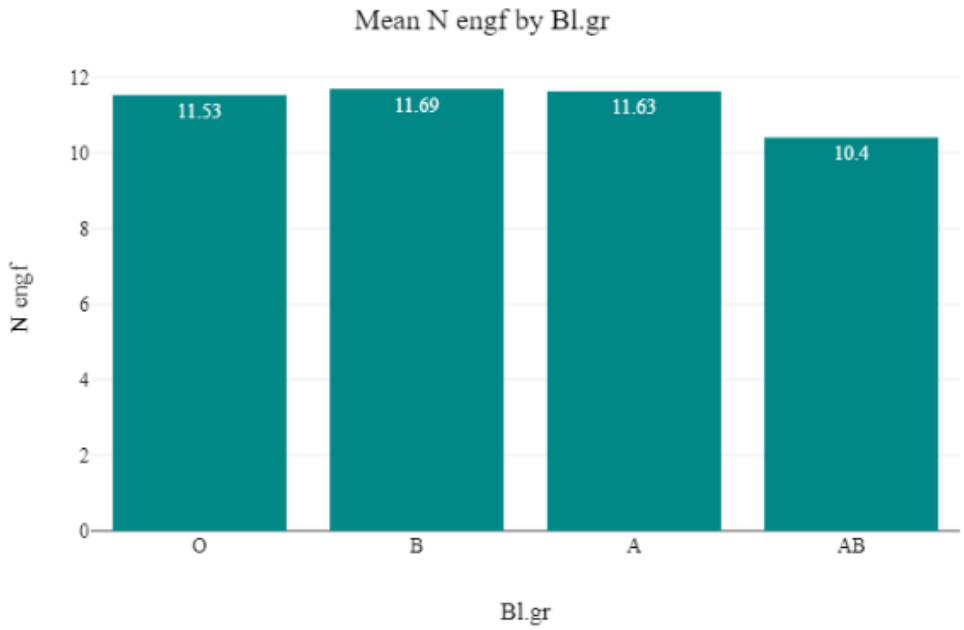


Figure 3 shows mean days of neutrophil engraftment in different blood group PBSC transplant patients.

The results of the descriptive statistics show that the 0 group (without cryopreservation) has higher values for the dependent variable neutrophil engraftment (N) (M = 11.57, SD = 2.36) than the 1 group (with cryopreservation) (M = 11.23, SD = 2.39). 5, 0 represent number of PBSC transplant without cryopreservation and 1 represent number of PBSCs transplant with cryopreservation.(Table – 5, figure-4)

Table-5 descriptive analysis of neutrophil engraftment in between cryopreserved versus non-cryopreserved PBSCs transplant.

		n	Mean	Std. Deviation	Std. Error Mean
N engf	0	30	11.57	2.36	0.43
	1	13	11.23	2.39	0.66

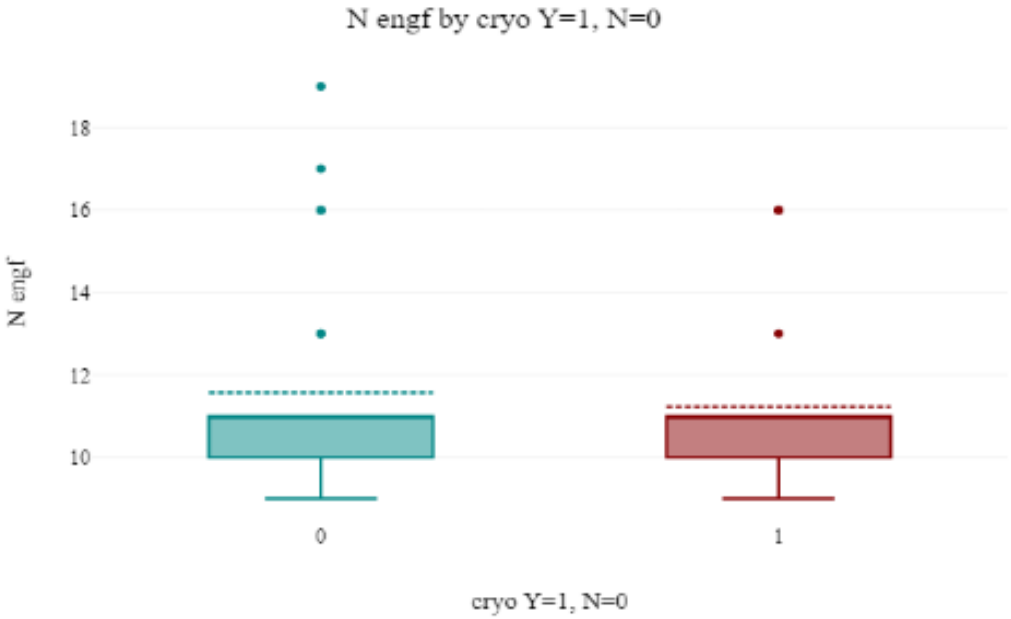


Figure 4: Green box represents without cryopreserved and red box represents with cryopreserved PBSCs transplantation.

The Levene test of equality of variance yields a p-value of 0.855, which is above the 5% significance level. The Levene test is therefore not significant and the null hypothesis that all variances of the groups are equal is retained. Thus, there is variance equality in the samples (Table-6).

Table 6 statistical analysis of two arms by Levene test

Test	F	df1	df2	P
Levene's Test (Mean)	0.03	1	41	.855
Brown-Forsythe-Test (Median)	0.24	1	41	.628

A two-tailed t-test for independent samples (equal variances assumed) showed that the difference between 0 and No with respect to the dependent variable neutrophil engraftment (N) was not statistically significant, $t(41) = 0.43$, $p = 0.671$, 95% confidence interval [-1.25, 1.92]. Thus, the null hypothesis is retained (Table-7)

Table- 7 calculation of p values for t-test for independent samples in two arms.

		t	df	p	Cohen's d
N engf	Equal variances	0.43	41	.671	0.14
	Unequal variances	0.43	22.64	.675	0.14

The results of the descriptive statistics show that the autologous PBSC transplant group has lower values for the dependent variable absolute neutrophil engraftment ($M = 10.45$, $SD = 0.83$) than the allogenic PBSC transplant group ($M = 15.22$, $SD = 2.44$) (Table-8, Figure-5)

Table- 8 shows descriptive statistical analysis of neutrophil engraftment in autologous versus allogenic PBSC patients.

		n	Mean	Std. Deviation	Std. Error Mean
N engf	auto	33	10.45	0.83	0.14
	allo	10	15.22	2.44	0.81

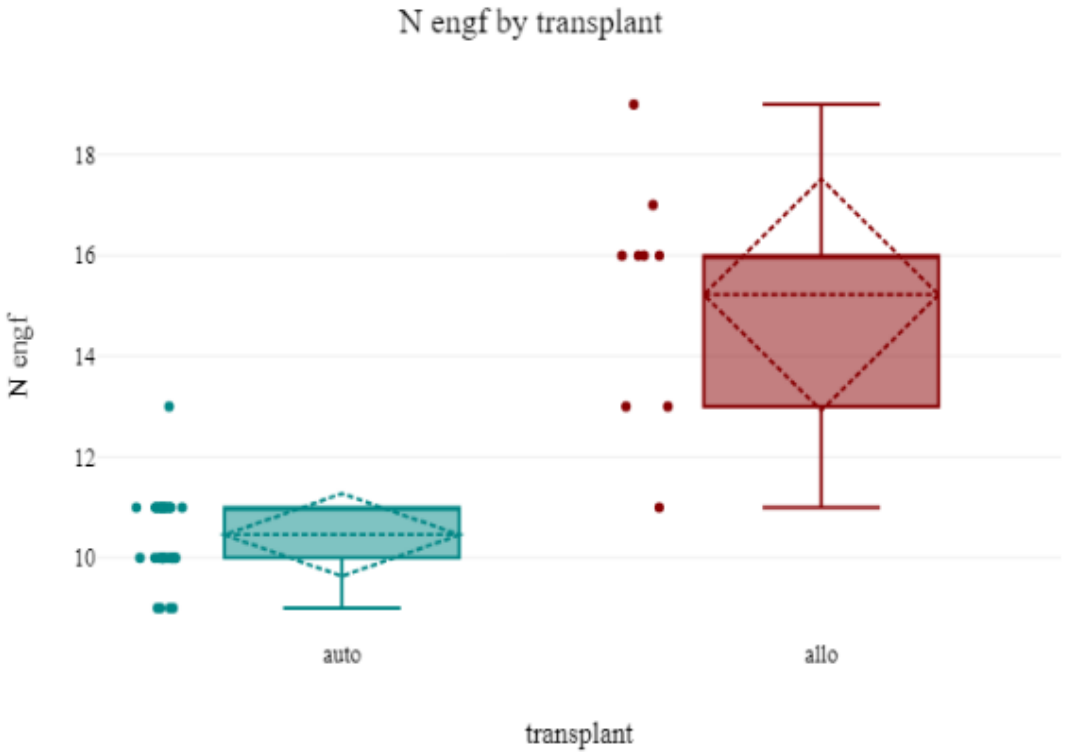


Figure 5: green box shows allogenic PBSCs, and red box shows autologous PBSCs transplant patients' neutrophil engraftment.

The Levene test of equality of variance yields a p-value of <.001, which is below the 5% significance level. The Levene test is therefore significant and the null hypothesis that all variances of the groups are equal is rejected. Thus, there is no variance equality in the samples (Table- 9).

Table -9 p value is < 0.001 by Levene test in comparative analysis in between two groups.

Test	F	df1	df2	p
Levene's Test (Mean)	20.85	1	40	<.001
Brown-Forsythe-Test (Median)	6.24	1	40	.017

A two-tailed t-test for independent samples (equal variances not assumed) showed that the difference between auto and allo with respect to the dependent variable N engf was statistically significant, $t(8.51) = -5.78$, $p = <.001$, 95% confidence interval [-6.65, -2.88]. Thus, the null hypothesis is rejected. Table-10.

Table-10 represents p value of neutrophil engraftment in comparison with two groups, p value is <0.001.

		t	df	p	Cohen's d
N engf	Equal variances	-9.6	40	<.001	3.61
	Unequal variances	-5.78	8.51	<.001	2.17

DISCUSSION

In the present study, statistical significance of '*p*' value was calculated among different parameters studied in 43 peripheral blood bone marrow transplant patients (PBSC).

The results showed that compared with G-CSF (n=30) alone, G-CSF plus plerixafor (n=13) was associated with significantly higher CD34+ cell yields, shorter apheresis sessions, and lower rates of mobilization failure. The study of Flomenberg N et.al. (2005) was like our present study [12].The median time to neutrophil engraftment was different between the two groups 11 (mean 12 ± 2.6 days) and 10 days (mean10.23±0.73 days) respectively. Comparative analysis of two groups by Mann-Whitney's test show significant statistical difference and '*p*' value was 0.018 which is ≤ 0.05. The time of neutrophil engraftment may also be influenced using medications (G-CSF and G-CSF+ Plerixafor) that stimulate the mobilization and production of CD34+ cells, which enhance the quality and quantity of collected stem cells results in faster engraftment.

Same study was conducted by Stiff P et al. for PBSC transplant using G-CSF alone and G-CSF plus plerixafor as a CD34+ mobilising agent, median days of neutrophil engraftment were 11 (8-16) days [13].

In the present study, neutrophil engraftment was compared with ABO blood groups (O=16, B=13, A=8, AB=6) among PBSC transplant patients. From the above-mentioned study '*p'* value was 0.765 calculated by t-test which was ≥ 0.05 and not statistically significant. Mean days of neutrophil engraftment according ABO blood group system given in Table-4 and Figure-3.

The association of neutrophil engraftment with ABO blood group system is not well-established.[14] Some studies have suggested that ABO mismatch may affect the time and durability of neutrophil engraftment, as well as the overall survival and non-relapse mortality of HSCT recipients[15] .However, other studies have found no significant difference in neutrophil engraftment or HSCT outcomes between ABO-matched and ABO-mismatched groups [16] Therefore, more research is needed to clarify the impact of ABO blood group system on neutrophil engraftment after HSCT.

In the present study comparative analysis was made in between two groups of PBSCs transplant patients. Non cryopreserved PBSCs (n=30) versus cryopreserved PBSCs (n=13) were statistically analysed and shows *p* value 0.855 by Levene test and 0.671 by 't' test, in both test *p* value is statistically insignificant (*p* value ≥ 0.05). The days of neutrophil engraftment was 11.59 ± 2.36 days in non-cryopreserved and cryopreserved was 11.23 ± 2.36 days respectively in PBSCs transplant patients.

The results showed that, there was no difference in time to neutrophil engraftment, incidence of infusion reactions, duration of hospitalization, progression-free survival, or overall survival between the two groups. However, cryopreservation also requires expensive equipment and trained personnel, and may cause adverse reactions due to DMSO infusion, such as nausea, vomiting, hypotension, and dyspnoea. In the present study out of 13 patients 3 had (23%) symptoms of nausea vomiting and dyspnoea after transfusion of thawed cryopreserved units. The average cost of ASCT was 10% lower in the non-cryopreserved group.

Two separate study was conducted from Thailand and Mexico, retrospectively and prospectively, there was no significant difference was observed of neutrophil engraftment in respect to non-cryopreserved versus non-cryo-preserved PBSCs transplantation. [17]

A comparative analysis of neutrophil engraftment in autologous versus allogeneic PBSC transplant can be done by looking at various factors, such as the number and quality of stem cells collected, the conditioning regimen, the graft-versus-host disease (GVHD) prophylaxis, and the outcome of the transplant [18]

In the present study, neutrophil engraftment was compared with autologous(n=33) versus allogenic (n=10) PBSCs transplant patients. Mean day of neutrophil engraftment was 10.45 days and 15.22 respectively in autologous and allogenic patients. From the above-mentioned study '*p'* value was calculated as < 0.001 by both Levene and t-test, which was ≤ 0.05 and statistically significant.

Morton James et al. 2001 conducted a study published in the blood journal, and he noticed that median time of neutrophil engraftment in allogenic PBSCs among 29 patients was 14 days [19]. However, there may be some differences between autologous and allogeneic PBSC transplant in terms of the optimal number of CD34+ cells (a subset of stem cells) infused, the risk of delayed engraftment, and the impact of donor factors on engraftment and survival[20,21].

CONCLUSION

For autologous and allogenic PBSC transplant neutrophil engraftment depends on various factors, such as mobilising agents, type of conditioning regime, presence, or absence of graft versus host disease and use of immunosuppressive drugs. In the

present study, it is observed single dose G-CSF versus G-CSF plus plerixafor mediates faster engraftment and which is statistically significant. The major limitation of this study was due to small number of samples.

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