Complications and the impact of hematological parameters in donors involved in allogenic peripheral blood stem cell transplantation for hematological malignancies

Complicações e o impacto dos parâmetros hematológicos em doadores envolvidos em transplante alogênico de células-tronco de sangue periférico para doenças hematológicas

Complicaciones e impacto de los parámetros hematológicos en los donantes que participan en un trasplante alogénico de células madre de sangre periférica por neoplasias hematológicas

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ABSTRACT
Hematopoietic stem cell transplantation (HSCT) is a vital treatment option for many hematological malignancies, offering a more convenient alternative to bone marrow transplantation. In allogeneic HSCT, donors provide hematopoietic stem cells for transplantation into patients, necessitating careful consideration of the donor's health and
hematological parameters to ensure successful engraftment and treatment outcomes. In a study involving 20 adult donors at Apeksha Hospital, Sri Lanka key hematological parameters, comorbidities, clinical histories, and medications were analyzed. Diabetes mellitus and hypertension were the most prevalent comorbidities among donors, while anemia, primarily linked to iron and vitamin B12 deficiencies, was common. Although baseline coagulation abnormalities were rare and no significant complications occurred during transplantation, early clinical issues such as pain and paresthesia correlated with abnormal peripheral blood smear findings. Notably, a 4-day single daily G-CSF dosing schedule was favored over a 5-day twice daily regimen due to fewer reported problems. While anemia and thrombocytopenia were infrequent, these findings underscore the critical importance of meticulous donor selection and vigilant monitoring throughout the transplantation process to optimize outcomes.

**Keywords:** hematopoietic stem cell transplantation, Allogeneic, G-CSF, donor.

**RESUMO**
O transplante de células-tronco hematopoéticas (TCTH) é uma opção de tratamento vital para muitas malignidades hematológicas, oferecendo uma alternativa mais conveniente ao transplante de medula óssea. No TCTH alogênico, os doadores fornecem células-tronco hematopoéticas para serem transplantadas em pacientes, o que exige uma consideração cuidadosa da saúde e dos parâmetros hematológicos do doador para garantir o sucesso do enxerto e dos resultados do tratamento. Em um estudo envolvendo 20 doadores adultos no Apeksha Hospital, Sri Lanka, foram analisados os principais parâmetros hematológicos, comorbidades, históricos clínicos e medicamentos. O diabetes mellitus e a hipertensão foram as comorbidades mais prevalentes entre os doadores, enquanto a anemia, principalmente ligada a deficiências de ferro e vitamina B12, era comum. Embora as anormalidades de coagulação na linha de base tenham sido raras e não tenham ocorrido complicações significativas durante o transplante, os problemas clínicos iniciais, como dor e parestesia, foram correlacionados com achados anormais de esfregaço de sangue periférico. Notavelmente, um esquema de dosagem de G-CSF de 4 dias, uma única vez ao dia, foi preferido em relação a um regime de 5 dias, duas vezes ao dia, devido a menos problemas relatados. Embora a anemia e a trombocitopenia não tenham sido frequentes, esses achados ressaltam a importância fundamental da seleção meticulosa do doador e do monitoramento vigilante durante todo o processo de transplante para otimizar os resultados.

**Palavras-chave:** transplante de células-tronco hematopoéticas, Alogênico, G-CSF, doador.

**RESUMEN**
El trasplante de células madre hematopoyéticas (TCMH) es una opción de tratamiento vital para muchas neoplasias hematológicas, ya que ofrece una alternativa más cómoda que el trasplante de médula ósea. En el TCMH alogénico, los donantes aportan células madre hematopoyéticas para su trasplante en pacientes, lo que requiere una cuidadosa consideración de la salud y los parámetros hematológicos del donante para garantizar el éxito del injerto y los resultados del tratamiento. En un estudio en el que participaron 20 donantes adultos del Hospital Apeksha de Sri Lanka, se analizaron parámetros hematológicos clave, comorbilidades, historias clínicas y medicación. La diabetes mellitus y la hipertensión fueron las comorbilidades más prevalentes entre los donantes, mientras que la anemia, relacionada principalmente con deficiencias de hierro y vitamina...
B12, era frecuente. Aunque las anomalías iniciales de la coagulación fueron escasas y no se produjeron complicaciones significativas durante el trasplante, los primeros problemas clínicos, como dolor y parestesias, se correlacionaron con resultados anormales del frotis de sangre periférica. En particular, se prefirió una pauta de dosificación de G-CSF diaria única de 4 días a una pauta de 5 días dos veces al día debido al menor número de problemas notificados. Aunque la anemia y la trombocitopenia fueron infrecuentes, estos resultados subrayan la importancia crítica de una selección meticulosa del donante y un seguimiento atento durante todo el proceso de trasplante para optimizar los resultados.

**Palabras clave:** trasplante de células madre hematopoyéticas, Alogénico, G-CSF, donante.

### 1 INTRODUCTION

Allogeneic peripheral blood stem cell transplantation is a crucial treatment modality for patients with hematological malignancies. The success of this procedure is influenced by various factors, including hematological parameters. Studies have shown that the infused total nucleated cell (TNC) dose and CD34+ cell dose play significant roles in transplant outcomes (Martin et al., 2016). Higher TNC doses have been associated with better survival rates in patients undergoing reduced-intensity allogeneic peripheral blood stem cell transplantation (Martin et al., 2016). Additionally, the impact of donor type on post-relapse survival has been investigated, highlighting the importance of donor selection in achieving favorable outcomes (Yr et al., 2016). Complications such as graft-versus-host disease (GVHD) can significantly impact the success of allogeneic stem cell transplantation (Morin-Zorman et al., 2016). Donor-specific anti-HLA antibodies have been identified as a factor contributing to early non-relapse mortality post-transplantation (Morin-Zorman et al., 2016). Furthermore, an impaired bone marrow microenvironment has been linked to poor graft function after allogeneic hematopoietic stem cell transplantation (Kong et al., 2013). The role of hematological parameters, such as ABO blood group incompatibility, has been a subject of study in allogeneic hematopoietic stem cell transplantation (Júnior et al., 2019). While conflicting evidence exists regarding the impact of ABO incompatibility on transplant outcomes, further research is needed to elucidate its significance (Júnior et al., 2019). The hematological parameters play a crucial role in determining the success and outcomes of allogeneic peripheral blood stem cell transplantation for hematological malignancies. Factors such as TNC and CD34+ cell doses, donor type, anti-HLA antibodies, and ABO blood group incompatibility can...
influence transplant outcomes and the occurrence of complications like GVHD and graft function. Understanding and optimizing these parameters are essential for improving the efficacy and safety of allogeneic stem cell transplantation in the treatment of hematological malignancies.

At the same time we need to focus on the donor as they can lead to several complications due to alteration of hematological parameters within the body after peripheral blood stem cell donation. In this study we mainly focus on the health state of the donor to improve the efficiency of this treatment in both aspects.

2 MATERIALS AND METHODS

The KDU Ethical Review Committee (RP/S/2022/14) approved the study, and the National Cancer Institute's director in Maharagama, Sri Lanka, gave authorization to carry out the research. The study included 20 adult donors who were connected to allogeneic peripheral blood hematopoietic stem cell transplantation (HSCTs) at the Apeksha Hospital's Bone Marrow Transplant Unit (BMTU). Donors were chosen using predetermined inclusion and exclusion standards. The study comprised donors who fulfilled the eligibility requirements for peripheral blood stem cell collection. Adult donors who meet the normal conditions for donation and are in good general health are often included in these criteria. However, to protect the study's integrity and the security of the transplant procedure, a few donors were left out. Donors who failed to meet the inclusion criteria, had insufficient information, or displayed pseudothrombocytopenia were among the exclusion criteria. The study sought to determine the best appropriate donor population by following these selection criteria to assess the influence of haematological factors on early problems in allogeneic peripheral blood stem cell transplantation.

2.1 DATA COLLECTION AND STATISTICS

Retrospective data collection was done using the donors' written and electronic records. Microsoft Excel 2013.12 and SPSS version 26 (Released 2017, IBM statistics for Windows version 26, IBM Corp., Armonk, NY) tools were used to tabulate and analyse the results, which were then organized into XL sheets. When presenting descriptive analyses for the ordinal and non-normally distributed data, medians and range
were used. The univariate analyses were conducted using Fisher exact, Mann-Whitney U, and Chi-square testing, if applicable, to identify variables linked to early problems. It was determined that a result was statistically significant when the p-value was less than 0.05. The potential components found by univariate studies were further incorporated into the logistic regression for the multivariate analysis (MVA).

Laboratory clinical decision limits and reference ranges for the hematological and biochemistry parameters were determined obtained according to the available literature. Other clinical decision limits for baseline laboratory values were defined according to recent publications and are given in Table 1 with baseline median values of the cohort.

Anemia is typically defined as a hemoglobin (Hb) level below 12 g/dL in females and below 13 g/dL in males, while polycythemia is characterized by Hb levels exceeding 16 g/dL in females and 16.5 g/dL in males (Augustsson, 2024; Finazzi et al., 2018). Leukocytosis is often identified by a white blood cell count above 10x10^9/L, and baseline neutropenia can be graded as mild (1.5x10^9/L), moderate (0.5-0.99x10^9/L), or severe (<0.5x10^9/L) (Schalet et al., 2022). Absolute monocytosis is typically defined as >1x10^9/L, and thrombocytopenia is recognized as platelet counts below 150x10^9/L (Batte et al., 2022; Miller et al., 2018). The limits for coagulation parameters are often determined based on bleeding risk studies, with a prolonged prothrombin time arbitrarily set at >14 seconds (Pozailov et al., 2023). High erythrocyte sedimentation rate (ESR) is defined as ESR exceeding half the age in males and half the age plus 10 in females (Koschade et al., 2021). Various ferritin levels have been defined for iron deficiency, with >300 μg/L in men and >200 μg/L in women considered hyperferritinemia (Dev et al., 2022; Itoh et al., 2021). Serum immunoglobulin (Ig) levels are also monitored in clinical practice. Complications on the day of apheresis, day 7 and day 30 were evaluated.

Table 1. Median values and clinical decision limits for laboratory parameters

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Median</th>
<th>Clinical decision limits</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hb*</td>
<td>14.5 gr/dL</td>
<td>Refer to text</td>
</tr>
<tr>
<td>(F):13.3 g/dL</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(M):15.4 g/dL</td>
<td></td>
<td></td>
</tr>
<tr>
<td>TLC*</td>
<td>7.06x10^9/L</td>
<td>4-10x10^9/L</td>
</tr>
<tr>
<td>ANC*</td>
<td>4.19x10^9/L</td>
<td>1.5-7x10^9/L</td>
</tr>
<tr>
<td>ALC*</td>
<td>2.15x10^9/L</td>
<td>0.5-5x10^9/L</td>
</tr>
<tr>
<td>AMC*</td>
<td>0.49x10^9/L</td>
<td>0.25-1x10^9/L</td>
</tr>
<tr>
<td>Platelet count</td>
<td>257x10^9/L</td>
<td>150-450x10^9/L</td>
</tr>
<tr>
<td>PT*, seconds</td>
<td>11.90</td>
<td>&gt;14</td>
</tr>
<tr>
<td>aPTT*, seconds</td>
<td></td>
<td>&gt;37</td>
</tr>
<tr>
<td>INR*</td>
<td>0.96</td>
<td>&gt;1.5 or &gt;1.3</td>
</tr>
<tr>
<td>Fibrinogen, mg/dL</td>
<td>311.5</td>
<td>200-450</td>
</tr>
<tr>
<td>ESR*, mm/h</td>
<td>7</td>
<td></td>
</tr>
</tbody>
</table>
Ferritin, µg/L
(F): 12
(M): 6
Refer to text

Vitamin B12, ng/L
(F): 26.1
(M): 71.1
<200: low
200-300: low-normal

Folate, ng/mL
(F): 26.1
(M): 71.1
<2: low
2.0-4: low-normal

Source: Prepared by the authors

3 RESULTS

Peripheral blood hematopoietic stem cell transplantation (HSCTs) was performed on 20 adult donors and the median follow-up duration was 12 months. There are 4 donors who had made a prior donation while most donors were making their first donation. Table 2 lists the donors' initial clinical and demographic information.

Table 2. Clinical and demographic variables of donors

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>n=20 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, median (range)</td>
<td>43 (18-81)</td>
</tr>
<tr>
<td>Female/Male</td>
<td>8/12</td>
</tr>
<tr>
<td>Comorbidities</td>
<td></td>
</tr>
<tr>
<td>- Diabetes Mellitus</td>
<td>3 (0.15%)</td>
</tr>
<tr>
<td>- Hypertension</td>
<td>5 (0.25%)</td>
</tr>
<tr>
<td>Anemia</td>
<td>9 (0.45%)</td>
</tr>
<tr>
<td>Personal/familial bleeding history</td>
<td>None</td>
</tr>
<tr>
<td>Personal/familial thrombosis history*</td>
<td>None</td>
</tr>
<tr>
<td>G-CSF² administration</td>
<td>19</td>
</tr>
<tr>
<td>Plerixafor administration</td>
<td>1 (0.05%)</td>
</tr>
<tr>
<td>Medications</td>
<td></td>
</tr>
<tr>
<td>- Iron (oral and intravenous)</td>
<td>8 (0.4%)</td>
</tr>
<tr>
<td>- Vitamin B12</td>
<td>5 (0.25%)</td>
</tr>
<tr>
<td>- ACEI/ARB⁴</td>
<td>4 (0.2%)</td>
</tr>
<tr>
<td>- Metformin</td>
<td>3 (0.15%)</td>
</tr>
<tr>
<td>- Low molecular weight heparin</td>
<td>1 (0.05%)</td>
</tr>
</tbody>
</table>

*One donor had family history of thrombophilia.
²Granulocyte-colony stimulating factor
⁴Angiotensin converting enzyme inhibitor/ angiotensin receptor blocker.
Source: Prepared by the authors

Among the donors, diabetes mellitus and hypertension were the most common comorbidities. Granulocyte colony stimulating factor, or G-CSF, was administered to the donors in accordance with two distinct protocols: 13 donors received a single daily dose over a period of 4 days, and 5 donors received twice daily dosing over a period of 5 days.
The other two donors were unaware of the G-CSF schedule. The donors had a number of baseline haematological problems. Compared to male donors (2.3%), female donors (5.1%) had a higher prevalence of anaemia. The distribution of etiological factors for anaemia comprised thalassemia trait in 1 donor (0.3%), isolated vitamin B12 deficiency in 3 donors (0.5%), combined iron and vitamin B12 deficiencies in 2 donors (5.9%), and an unknown aetiology in 1 donor (0.3%). Additionally, 3.2% of the donors had baseline polycythemia.

When it came to coagulation markers, 3 donors (0.9%) had increased international normalised ratio (INR) values, 1 donor (0.3%) had an activated partial thromboplastin time (aPTT) longer than 37 seconds, and 7 donors (0.8%) had prothrombin times (PT) longer than 14 seconds. Two donors (0.8%) had hypofibrinogenemia, while 3 donors (7.5%) had hyperfibrinogenemia. Ferritin levels were measured in order to evaluate nutritional anaemia. Ferritin values below 15 µg/L were found in 5 donors (13%) and below 30 µg/L in 6 donors (31%), and below 100 µg/L in 8 donors (0.3%) and 6 donors (2%) had hyperferritinemia. Of the donors, 5(0.25%) had low levels of vitamin B12, and no one had low-normal levels. One donor (0.3%) had low folate levels, while 9 donors (3.1%) had low-normal folate levels. 8 donors (2.7%) had various blood abnormalities, such as granulocytosis, eosinophilia, anisopoikilocytosis, and hypochromia. The peripheral smears of the remaining donors were normal. Eight donors underwent haemoglobin electrophoresis, and all of them tested normal. Only one donor, who was suspected of having beta thalassemia trait, was not tested. Ultimately, at baseline, the immunoglobulin levels of just 6 donors were examined, and all of them were found to be within normal ranges. There are 20 peripheral blood HSCT donors did not require any transfusions. Table 3 lists the early clinical problems that were reported in each of the eight donors.

<table>
<thead>
<tr>
<th>Complication</th>
<th>Grade 1-2 (n)</th>
<th>Grade 3-4 (n)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypokalemia</td>
<td>1</td>
<td>None</td>
</tr>
<tr>
<td>Hypotension</td>
<td>1</td>
<td>None</td>
</tr>
<tr>
<td>Limbal immune conjunctivitis</td>
<td>1</td>
<td>None</td>
</tr>
<tr>
<td>Pain</td>
<td>3</td>
<td>None</td>
</tr>
<tr>
<td>Paresthesia (temporary)</td>
<td>None</td>
<td>1</td>
</tr>
</tbody>
</table>

Source: Prepared by the authors
None of the donors reported experiencing any of the other possible side effects, which include fever, lightheadedness, exhaustion, nausea, rash, injection site responses, appetite loss, haemorrhage, catheter problems, vomiting, syncope, shortness of breath, and thrombosis. Hypotension, hypokalemia, and limbal conjunctivitis were not observed to be significantly associated with any of the baseline clinical or haematological variables. Nonetheless, there was a significant correlation between baseline peripheral blood smear abnormalities and complaints of discomfort (11.5% vs. 0.4%, p=0.012, RR 40.1, 95% CI 2.2-709). Clinical problems were found to be substantially more common in donors with abnormal baseline peripheral smears than in those with normal peripheral smears (25% vs. 1.4%, p=0.009). Furthermore, compared to donors who received 4 days of single daily G-CSF dose, problems were more likely in those who received 5 days of twice daily G-CSF treatment (8.9% vs. 0.4%, p=0.000). Five days of twice-daily G-CSF dosage was found to be an independent risk factor (p=0.015, RR 16.8, 95% CI 1.7-165.9) in multivariate analysis for the development of clinical problems.

During the study period, there were no cases of grade 3–4 anaemia (Hb <8 gr/dL) related to early problems in laboratory examinations. On the day of apheresis, white blood cell differentials and total leukocyte counts were not measured. While leukocytosis (>10*10^9/L) and neutrophilia (>7*10^9/L) were assessed. On the day of apheresis, donors with baseline anaemia (12% vs. 0.7%, p=0.003) and those with baseline INR >1.3 (50% vs. 1.4%, p=0.035) were substantially more likely to have anaemia of any grade. Based on multivariate analysis, baseline anaemia was identified as an independent risk factor (p=0.003, RR 20.6, 95% CI 2.6-131.5) for the development of any grade of anaemia on the day of apheresis.

The donors who had higher than median baseline Hb levels (4.3% vs. 0%, p=0.016), baseline lymphopenia (50% vs. 2%, p=0.045), baseline INR >1.3 (50% vs. 2.1%, p=0.049), and those who received five days of twice-daily dosing G-CSF (7.8% vs. 0.4%, p=0.001) were significantly more likely to have haemoglobin levels ≥2g/dL on the day of apheresis compared to baseline. A haemoglobin drop of ≥2g/dL on the day of apheresis was independently associated with 5 days of twice daily dosing G-CSF (p=0.005, RR 26.5, 95% CI 2.7-259.1) in multivariate analysis.

On the day of apheresis, donors with baseline leukopenia (33.3% vs. 0.6%, p=0.029) and baseline lymphopenia (50% vs. 0.7%, p=0.019) were substantially more likely to experience any grade of thrombocytopenia (<75*10^9/L). None of these variables were shown to be significantly associated with the development of any grade of
thrombocytopenia on the day of apheresis in multivariate analysis.

4 DISCUSSION

Anaemia was a prevalent problem among the group of 20 donors of peripheral blood hemodialysis. As of right now, recommendations state that donation is acceptable in cases of mild anaemia or after correction in cases of more severe anaemia. Neither of the two donors developed early problems despite having anaemia associated with either an iron or vitamin B12 deficiency. In this group, iron and vitamin B12 deficiency were the most common causes of anaemia, both of which are treatable. Iron deficiency was indicated by low ferritin levels in 31% of the donors. While some donors received vitamin B12, others received iron supplements.

Donors are considered appropriate in cases of secondary polycythemia if their hematocrit (Htc) is less than 52% in males and less than 48% in women. Haemoglobin measures in this investigation indicated polycythemia, even though hematocrit values were not noted. There was insufficient information to differentiate between primary and secondary polycythemia. Moreover, no data on smoking was gathered. However, polycythemia did not appear to be associated with any early donor problems.

The most common abnormalities of white blood cells at baseline were leukocytosis and neutrophilia, but there was no significant correlation seen between these and early problems. In the cohort, baseline thrombocytopenia was infrequent. As long as there are no contraindications, donors with mild thrombocytopenia (100–130x10³/L) may be considered eligible. In the trial, no donor's platelet count was lower than 130*10⁹/L.

Abnormalities in basal coagulation were rare and were only found in laboratory testing. Haemophilia and other bleeding disorders were not present in the cohort's cases. Because thrombophilia runs in the family, one donor took low molecular weight heparin, but no bleeding problems happened. The most recent recommendations state that donors who have secondary polyglobulinemia are acceptable in terms of donor eligibility. For the few donors for whom this information was available, baseline immunoglobulin levels were within normal ranges.

The most frequent early clinical consequences were pain and paresthesia, which were both associated with aberrant peripheral blood smear findings. It's unclear, though, whether this association has any therapeutic significance. Due to a decreased incidence...
of problems, a 4-day single daily G-CSF schedule may be more appropriate than a 5-day twice daily dosage protocol. On the day of apheresis, thrombocytopenia and a drop in haemoglobin are the most worrisome conditions. Anaemia and thrombocytopenia were uncommon but happened to the group on the day of apheresis. It is not surprising that there is a correlation between baseline anaemia and anaemia on the day of apheresis; this means that collection should be postponed until anaemia is repaired. The choice of a 4-day single daily dose schedule is further supported by the remarkable link found between haemoglobin decrease on the day of apheresis and the 5-day twice daily dosing G-CSF.

4.1 LIMITATIONS

There were only limited number of donors were complete blood counts recorded on day 7, despite the observation of reductions in haemoglobin levels, leukocytosis, and neutropenia. If more donors were tracked down after making a donation, more noteworthy conclusions might be reached and increase the validity of the study. The minimal number of donors with follow-up data beyond the day of apheresis constituted a significant study constraint. Furthermore, it's possible that donor records underreported clinical difficulties due to the study's retrospective design. In order to solve this issue better to conduct this study with large cohort, prospectively at multicenter.

5 CONCLUSION

Haematological problems are frequently found when evaluating possible donors. An iron shortage is a common issue. Stem cell collection for anaemic donors should be considered only after the anaemia has been treated. On the day of apheresis, extra care should be taken to manage the anaemia. Arranging G-CSF schedule on 4-day, single-daily could reduce the likelihood of early problems and increase donation process safety.
REFERENCES


Diseases, 67(6), 813-816. https://doi.org/10.1093/cid/ciy584


