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Role of Bedside Leukoreduction Filters in Mitigating Febrile Non-Hemolytic Transfusion Reactions in Thalassaemia Major Patients: Clinical Experience from a Public-Sector Hospital

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Author`s Contribution

[1-3] Substantial contributions to the conception or design of the work; or the acquisition, analysis, or interpretation of data for the work, [4,5]Active participation in active methodology, analysis, or interpretation of data for the work, [6]Drafting the work or revising it critically for important intellectual content

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ABSTRACT

Objective: To evaluate the clinical effectiveness of bedside leukoreduction filters in reducing the occurrence of febrile non-hemolytic transfusion reactions (FNHTRs) among patients with beta-thalassemia major, by comparing their frequency in patients receiving blood through a filter versus those without a filter.

Methodology: A retrospective cross-sectional comparative study was conducted at the Thalassemia Centre in collaboration with the Blood Bank, Pakistan Institute of Medical Sciences, from January to March 2024. A total of 1,000 multi-transfused beta-thalassemia major patients with a history of FNHTRs were included and divided into two groups: 500 patients received blood through bedside leukoreduction filters, while 500 received non-filtered blood. Transfused red cell concentrates ranged in storage age from 2 to 14 days. Data were analyzed using SPSS Version 20, and the chi-square test was applied to compare the incidence of FNHTRs between the two groups. A p-value of <0.05 was considered statistically significant.

Results: Among the 500 patients receiving bedside leukoreduced blood, 7 (1.4%) experienced FNHTRs during transfusion, presenting with symptoms such as fever, chills, cold extremities, abdominal pain, and facial flushing. In contrast, 49 (9.8%) patients receiving non-filtered blood developed FNHTRs ($p < 0.001$).

Conclusion: The incidence of FNHTRs was significantly reduced with the use of bedside leukoreduction filters compared to non-leukoreduced blood. Implementing this simple and cost-effective strategy in resource-limited settings can help prevent transfusion reactions, improve patient and staff satisfaction, and reduce the risk of transfusion discontinuation, prolonged hospitalization, and extensive laboratory investigations.

Keywords: Beta-thalassemia major, Febrile non-hemolytic transfusion reactions, Leukoreduction filters, Bedside leukoreduction.

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Introduction

Leukocyte contamination in blood components can lead to various harmful transfusion-related effects, such as febrile non-hemolytic transfusion reactions (FNHTRs), transfusion-related immunomodulation, allergic reactions, transfusion-related acute lung injury, transfusion-transmitted infections etc. Different methods for leukoreduction include washing with normal saline, buffy coat removal, differential centrifugation, and leukocyte filtration. Among these, leukofiltration is the most effective, achieving a leukocyte count reduction of 3 to 4 logs.[1] This works by trapping the undesirable leukocytes, and allowing the passage of desired blood products.[2] In particular, leukoreduction reduces the risk of three types of reactions; FNHTRs, HLA-alloimmunization and transfusion-transmissible cytomegalovirus infection. In the United States of America, most of the cellular blood components are leukoreduced before storage to minimize these reactions.[3]

The differential diagnosis for fever caused by a transfused blood product includes FNHTR, transfusion-transmitted infection (TTI), transfusion-associated acute lung injury (TRALI), and acute hemolytic transfusion reaction (AHTR). It is essential to correlate the signs and symptoms suggestive of a transfusion reaction with the patient's underlying clinical history.[4]

Febrile non-hemolytic transfusion reactions are frequent non-infectious complications associated with transfusing allogeneic RBCs. In one study, FNHTR was the most frequently reported reaction (0.36% incidence), followed by allergic reactions.[5] These reactions commonly occur during the transfusion process but can also present within 4-6 hours post-transfusion. The occurrence rate of febrile reactions in non-leukoreduced red cells is estimated to range from 0.5% to 6.8% of all transfused units. FNHTRs are mostly self-limiting and characterized by a temperature rise of over 1°C, along with chills and rigors. Additional symptoms, such as nausea, vomiting, dyspnea, and hypotension, may also occur, but they are not typically considered life-threatening.[6]

In patients with Beta Thalassemia Major who receive chronic transfusions, Febrile Non-Hemolytic Transfusion Reaction is a significant complication. These reactions are triggered by the recipient's immune response to the donor's leukocytes. Leukodepletion, which involves removing leukocytes from donated blood, can be carried out during the collection of blood, at the level of blood processing or at bedside.[7] ensuring RBC units contain less than 5 x 10^6 leukocytes.[8]

Most studies in the literature have focused on the use of pre-storage leukoreduction for preventing febrile non-hemolytic transfusion reactions (FNHTRs) in patients with specific risk factors. However, in resource-limited settings, such as government institutions, implementing this strategy can be challenging due to financial constraints. In such cases, a more cost-effective alternative, such as post-storage leukoreduction using bedside filters, may help reduce the burden of febrile transfusion reactions. This study aimed to assess the clinical effectiveness of bedside leukoreduction filters in reducing the occurrence of FNHTRs among patients with beta-thalassemia major.

Methodology

It was a retrospective, cross-sectional, comparative study conducted at the Thalassemia Centre in collaboration with the Blood Bank, Pakistan Institute of Medical Sciences (PIMS), Islamabad, from January to March 2024. The sampling technique used was consecutive non-probability sampling. The sample size was calculated using the WHO calculator with the following parameters: confidence level = 95%, margin of error = 5%, population proportion = 50%, and population size = 120.[7], yielding a minimum required sample size of 92. However, we included 500 patients in the study who received red cell concentrates (RCC) through bedside leukoreduction filters. For comparison, a control group of 500 beta-thalassemia major patients was recruited, who received RCC without a filter.

All participants had a confirmed diagnosis of transfusion-dependent beta-thalassemia major and a documented history of FNHTRs during previous transfusions. Both male and female patients, including pediatric and adult age groups, were included. Patients who were recently diagnosed with beta-thalassemia major or those with no known previous history of FNHTRs were excluded from the study.

After approval from IRB, Ref F.1-1/2015/ERB/SZABMU/1228, data record of all beta thalassemia major patients fulfilling the inclusion criteria receiving red cell concentrate transfusions through bedside leukoreduction filters was noted. Similarly, the data of patients who did not receive leuko-reduced blood (control group) was also recorded. No pre-transfusion medicines were given to any patient. Specific filters that reduce the WBC count provided by PuriBlood filters by Innovative Medical Manufacturing Company, Taiwan, were used at the bedside in thalassemia centre for transfusion of red cell concentrates. Informed consent performa was filled at the time of transfusion from each patient's attendant. The data analyzed included demographic details like age, gender, pretransfusion and post-transfusion vital signs, any adverse event noted alongwith the clinical signs and symptoms. Adverse transfusion events characterized by the onset of fever during or within 24 hours after a blood transfusion, excluding other identifiable causes of fever. These reactions typically involve an increase in body temperature of ≥1°C (1.8°F) from baseline and may be accompanied by chills, rigors, and other systemic symptoms. Their non-hemolytic nature was confirmed by laboratory evidence confirming the absence of significant hemolysis, such as a stable hemoglobin level, absence of hemoglobinuria, and negative Coomb's test. Resolution of fever and associated symptoms upon discontinuation of the transfusion support a causal relationship between the transfusion and the febrile reaction. The data was

analyzed using SPSS version 20. Qualitative and Quantitative variables were measured by using descriptive statistics. Qualitative variables such as gender, number of patients, number of patients experiencing any adverse event in the form of FNHTR, signs/symptoms of any adverse event, filter failure, medication given were expressed in terms of percentages.

Quantitative variables for example mean age of patients and gender distribution were measured as Mean ± Standard Deviation or percentages. Qualitative variables were represented as Bar or Pie charts. Comparison was done between the two groups of patients, in terms of frequency of FNHTR noted. Chi-square test was employed to compare the FNHTR incidence between filtered vs. non-filtered groups. A p value less than 0.05 was considered significant.

Results

A total of 1000 patients (500 who received blood through a filter, and 500 who received blood without a filter) were included in the study. The gender and age distributions of patients in both groups are depicted in Figures 1 & 2. The age range of patients enrolled in study was 2-37 years with a mean age of 10.5 ± 5.7 years in the filter group and 8.54 ± 3.17 years in the non-filter group.

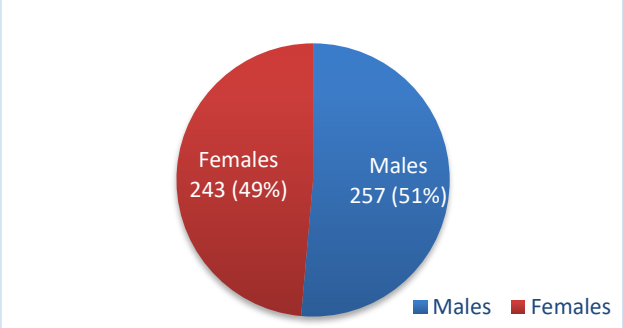

Figure 1. Gender distribution of patients receiving blood through bedside leukoreduction filter.

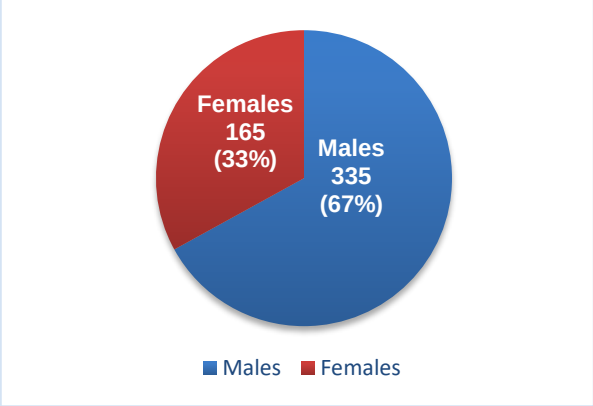

Figure 2. Gender distribution of patients receiving blood without a filter

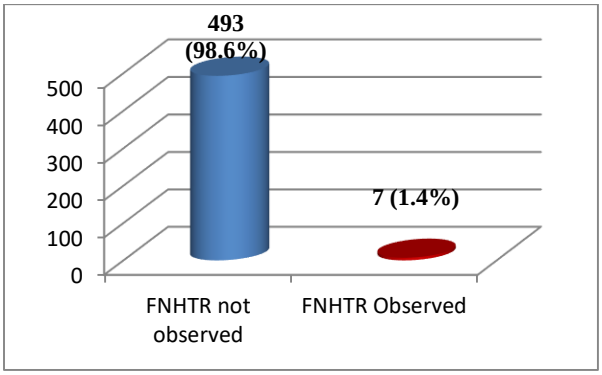

Figure 3. Frequency of FNHTR following Transfusion using Bed-side Leukoreduction Filter

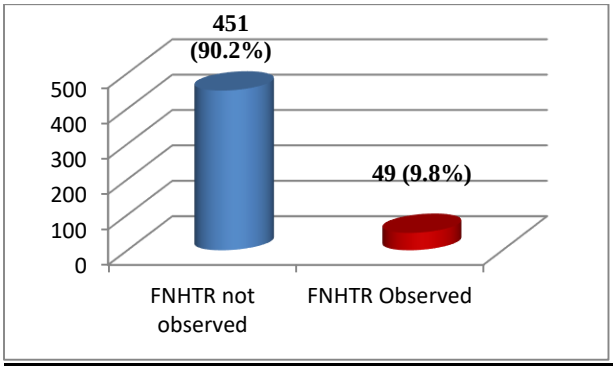

Figure 4. Frequency of FNHTR following Transfusion without using a leukoreduction filter.

Transfused red cell concentrates varied in age from 2-14 days. We observed that the majority of our patients i.e. 493/500 (98.6%), who received blood through a bedside leukoreduction filter did not experience FNHTR during or after transfusion. Only 7(1.4%) patients faced one or more signs or symptoms suggesting the occurrence of FNHTR. (Figure 3), In the control group, for whom leukoreduction filter was not employed, 49 (9.8%) patients experienced FNHTR signs and symptoms. (p value <0.001) Figure 4. Common symptoms experienced by patients were fever, chills, headache, nausea and vomiting. Common clinical signs observed were rise in temperature and tachycardia.

Discussion

Leukocytes are a component of human blood that play a key role in defense against bacterial infections. However, donor leukocytes in transfused blood products can lead to various adverse reactions in the recipient, including febrile non-hemolytic transfusion reactions, alloimmunization with human leukocyte antigen and platelet refractoriness. They can also be a source of

transmission for infectious agents, such as cytomegalovirus.[9] FNHTR is among the most frequently observed transfusion reactions, occurring at a rate of 86.4/100,000 transfused units. The suspected pathophysiology involves cytokines released by white cells present in stored blood components. Leukoreduction, a modification process that removes white blood cells from blood products, is an effective method for reducing the incidence of FNHTR.[10] A previous study indicated that HLA-mediated antigen-antibody reactions are a trigger for FNHTR.[11]

FNHTR most commonly occurs in recipients who have undergone repeated transfusions.[12] Patients may develop HLA antibodies after multiple blood transfusions or, in women, following pregnancy. Upon subsequent transfusions, these antibodies can react with transfused leukocytes or platelets, leading to the release of pyrogens and causing fever and further symptoms. Additionally, if the donors possess HLA antibodies, these can be transferred to recipients during transfusion, potentially resulting in febrile reactions.[11] Blood filtration to remove these leukocytes can be performed during the processing stage, after processing, or at the time of transfusion.[13]

Our study found that the use of bedside leukoreduction filters significantly reduced the incidence of FNHTRs in thalassemia major patients who undergo multiple transfusions from an early age. These findings are consistent with the limited available literature, which suggests that bedside leukoreduction effectively reduces FNHTRs by minimizing the leukocyte load in transfused blood—a known trigger for these reactions. One major concern with FNHTRs is the need for immediate cessation of transfusion to exclude hemolytic reactions. Although FNHTRs are generally benign, the implicated blood units are typically discarded, resulting in additional financial burden for healthcare facilities.

Currently, pre-storage leukoreduction is favored, either through universal leukoreduction for all patients or selective leukoreduction for specific patient groups. The main drawback of universal leukoreduction is its high cost. On the other hand, selective leukoreduction presents challenges in inventory management, as predicting the need for leukoreduced blood components during preparation is difficult. In contrast, bedside leukoreduction can be selectively performed for patient groups that require leukoreduced blood components. However, studies have shown that bedside leukoreduction is not as effective as pre-storage leukoreduction in reducing the adverse effects of leukocytes.[14]

In a study, the incidence of FNHTRs significantly decreased with pre-storage leukoreduced RBCs. In vitro studies showed elevated levels of cytokines like IL-1β and IL-8 in post-storage RBCs. These findings suggest that pre-storage leukoreduction reduces the accumulation of cytokines, thereby decreasing transfusion-associated adverse reactions.[15] In another study, pre-storage leukoreduced apheresis platelets significantly reduce the occurrence of febrile non-hemolytic transfusion reactions compared to post-storage groups.[16] Another study concluded that pre-storage leukoreduction reduced FNHTR from RBC units from 0.24% to 0.05%.[17]

While most current studies focus on pre-storage filters, our study contributes for valuable data on effectiveness of bedside filters. Limited data is available for bedside filters. A study by Waheed et al.[18] on thalassemia major cases reported a 26.3% incidence of transfusion-associated reactions in 2193 red cell transfusions. FNHTR was found out as the most common reaction. A study by Nasir et al.[7] found that the use of bedside filters eliminated FNHTRs, reducing the reaction rate to 0% in cases that previously had a high incidence. Conversely, using non-leukoreduced blood resulted in a 100% occurrence rate of FNHTRs. This demonstrates that bedside-filter leukoreduction significantly reduces FNHTRs compared to non-leukoreduced blood.

Leukoreduction in thalassemic patients can be effective in preventing transfusion reactions. In a study from India by Devi et al., which assessed the leukodepletion status of blood products and associated transfusion reactions in thalassemic patients, reactions were observed in 3 (0.2%) out of 161 patients. Two reactions occurred with leukoreduced (buffy-coat method) transfusions, and one with non-leukoreduced PRBC. Notably, no reactions were observed in transfusions using bedside filters for leukodepletion. The study concluded that bedside filter leukodepletion is more effective in preventing transfusion reactions.[19]

Similarly, a study from Malaysia evaluated the efficacy of leukocyte removal using two different filters during bedside transfusions for patients with transfusion-dependent thalassemia. The study included 51 transfusion events, randomly using either a non-woven polyester filter or a polyurethane filter. The polyurethane filter achieved 98.4% leukocyte removal, while the polyester

filter achieved 96.2% (p = 0.022). No adverse events or transfusion reactions were reported in their study.[20]

Our study demonstrates that bedside filters—though less commonly studied in the current era of universal pre-storage filtration—also significantly reduce FNHTRs and provide a cost-effective solution in resource-limited settings. Where pre-storage filtration is not feasible due to higher costs, bedside filtration offers a practical and economical alternative, as evidenced by our results. This strategy may serve as a viable option to improve transfusion safety in such settings.

The main strengths of our study were that it had a large sample size, enhancing reliability of our findings, The limitations of my study were that it was carried out at one point of time, with a lack of follow-up to determine trend of reactions in subsequent transfusions. Moreover, small number of studies are available for direct comparison highlighting the need for future studies in this area. According to findings of my study, implementing this practical strategy in resource-constrained settings may prove advantageous in preventing transfusion reactions, enhancing patient and staff satisfaction, reducing the risks of discontinuation of transfusion, prolonged hospital stay and the need for laboratory evaluation. This evidence further suggests the potential extension of this approach to other patient populations, including multiparous females and leukemia patients requiring transfusions. Future long-term prospective studies in terms of both cost-effectiveness and clinical outcomes are required to provide a more comprehensive analysis.

Conclusion

The frequency of FNTHR in thalassemic patients is significantly low when they are transfused bedside-filtered leukoreduced blood.

References

1. Sheikh MA, Biswas AK, Baranwal AK, Kushwaha N, Karade S, Philip J. Comparative study of quality of leukoreduced packed red blood cell units as assessed by nageotte hemocytometry and flow cytometry. Asian Journal of Transfusion Science. 2023;17(1):63. doi: 10.4103/ajts.AJTS_101_21.
2. Ferdowsi S, Abbasi-Malati Z, Pourfathollah AA. Leukocyte reduction filters as an alternative source of peripheral blood leukocytes for research. Hematol Transfus Cell Ther. 2021;43(4):494-498. doi: 10.1016/j.htct.2020.10.963. Epub 2020 Dec 24. PMID: 33422490; PMCID: PMC8573042.
3. Raval JS, Griggs JR, Fleg A. Blood Product Transfusion in Adults: Indications, Adverse Reactions, and Modifications. Am Fam Physician. 2020;102(1):30-38.
4. Shmookler AD, Flanagan MB. Educational Case: Febrile Nonhemolytic Transfusion Reaction. Acad Pathol. 2020;7:2374289520934097. doi: 10.1177/2374289520934097.
5. Kaleemi S, Humayun L, Salahuddin H, Arif F, Akhtar A, Nasir A. Adverse blood transfusion reaction in tertiary care hospitals: an initiative towards improvement: a multi-center study. Proceedings S.Z.M.C [Internet]. 2022;36(2):40-45. https://doi.org/10.47489/PSZMC-836362-40-45
6. Rajesh K, Harsh S, Amarjit K. Effects of Prestorage Leukoreduction on the Rate of Febrile Nonhemolytic Transfusion Reactions to Red Blood Cells in a Tertiary Care Hospital. Ann Med Health Sci Res. 2015;5(3):185-188. doi: 10.4103/2141-9248.157498.
7. Nasir K, Waheed U, Tahir S, Zaheer HA. Leucodepletion in Thalassaemia Major Patients in Pakistan. Journal of Islamabad Medical & Dental College. 2018;7(3):157-158.
8. Dejigov Monteiro da Silva N, Nukui Y, Takahashi J, de Almeida Lopes Monteiro da Cruz D, de Souza Nogueira L. Effect of post-storage filters vs. pre-storage filters for leukoreduction of blood components on clinical outcomes: a systematic review and meta-analysis. Syst Rev. 2024;13(1):196. doi: 10.1186/s13643-024-02615-z.
9. Chand S, Rudrappan RB, Gupta D. Leukoreduced red cell concentrates: Are they meeting the quality standards? Asian J Transfus Sci. 2023;17(2):151-156. doi: 10.4103/ajts.ajts_126_21.
10. Khan AI, Gupta G. Noninfectious Complications of Blood Transfusion. [Updated 2023 Aug 8]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2024 Jan-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK574536/
11. Wang H, Ren D, Sun H, Liu J. Research progress on febrile non-hemolytic transfusion reaction: a narrative review. Ann Transl Med. 2022;10(24):1401. doi: 10.21037/atm-22-4932.
12. Gelaw Y, Woldu B, Melku M. Proportion of Acute Transfusion Reaction and Associated Factors Among Adult Transfused Patients at Felege Hiwot Compressive Referral Hospital, Bahir Dar, Northwest Ethiopia: A Cross-Sectional Study. J Blood Med. 2020;11:227-236. doi: 10.2147/JBM.S250653.
13. Urias EVR, Teles LF, Lula JF, Rocha CU, Pereira IA, Givisiez FN, et al. Leukocyte filters: a review of the mechanisms and applications in hemotherapy. Rev Assoc Med Bras (1992). 2021;67(7):1056-1060. doi: 10.1590/1806-9282.20210383.
14. Sharma RR, Marwaha N. Leukoreduced blood components: Advantages and strategies for its implementation in developing countries. Asian J Transfus Sci. 2010;4(1):3-8. doi: 10.4103/0973-6247.59384.
15. Chang CC, Lee TC, Su MJ, Lin HC, Cheng FY, Chen YT, et al. Transfusion-associated adverse reactions (TAARs) and cytokine accumulations in the stored blood components: the impact of prestorage versus poststorage

leukoreduction. Oncotarget. 2017;9(4):4385-4394. doi: 10.18632/oncotarget.23136.

16. Chien SH, Huang HY, Chen YJ, Tsai YC, Lu SH, Lee LH, et al. Comparing transfusion reactions between pre-storage and post-storage leukoreduced apheresis platelets: an analysis using propensity score matching. Ann Hematol. 2024;103(4):1389-1396. doi: 10.1007/s00277-024-05652-9.
17. King KE, Shirey RS, Thoman SK, Bensen-Kennedy D, Tanz WS, Ness PM. Universal leukoreduction decreases the incidence of febrile nonhemolytic transfusion reactions to RBCs. Transfusion. 2004;44(1):25-9. doi: 10.1046/j.0041-1132.2004.00609.x. PMID: 14692963.
18. Waheed U, Wazeer A, Qasim Z, Iqbal Z, Zaheer HA. Surveillance of Adverse Transfusion Reactions in Multi-transfused Thalassaemia Patients in Mirpur, Azad Jammu and Kashmir, Pakistan. Annals of PIMS.2016; 12(1):27-30
19. Shanthala Devi AM, Gaikhonlungpou KG. Leukodepletion status of blood products and transfusion reactions in thalassemic patients. J Appl Hematol 2014;5:29-31.
20. Jamal R, Mazeni NR, Hussin H. Evaluation of two types of leukocyte removal filters on transfusion dependent thalassaemics. Malays J Pathol. 2000;22(2):79-83.