

Effectiveness of Bedside Leucodepletion Filter in Multi-Transfuse Thalassemia Patients

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ABSTRACT

Multi-transfused thalassemia patients are prone to transfusion-related complications. Febrile nonhemolytic transfusion reactions (FNHTR) are a relatively common complication associated with allogenic transfusions. As leucocytes have been implicated in the mechanism of FNHTR, it has been proposed that the transfusion of leucodepleted RBCs should be associated with a decreased incidence of FNHTR. Currently, the best leucodepletion can be achieved using leucodepletion filter. A quasi-experimental study was carried out between March 2019 and August 2021 in the Department of Transfusion Medicine of Bangabandhu Sheikh Mujib Medical University (BSMMU), Dhaka, Bangladesh, to evaluate the effectiveness of bedside leucodepletion filter in decreasing febrile nonhemolytic transfusion reactions (FNHTR) in multi-transfused thalassemia patients. We adopted a purposive sampling method. A total of 84 transfusion dependent thalassemia patients were included in this study according to inclusion and exclusion criteria and divided equally into two groups – intervention group and comparison group. Allocation of intervention was performed by non-randomized alternate assignment. The intervention group received packed red blood cells using leucodepletion filters, while the comparison group received packed red blood cells with conventional blood transfusion filters. The incidence of FNHTR was evaluated between these two groups. The mean age was 19.11±16.54 years in the intervention group and 15.79±10.83 years in the comparison group. Females were predominant in both groups, i.e., 59.5% and 54.8% in intervention group and comparison group respectively. Among adverse reactions, 21(25%) of the patients experienced chills and rigors – 2(4.8%) in the intervention group and 19(45.2%) in the comparison group. Other symptoms were only observed in the comparison group such as fever (38.1%), vomiting (4.8%), myalgia (7.1%), hypotension (2.4%) and skin rash (2.4%). Only 2(4.8%) patients had FNHTR in intervention group, while 25(59.5%) in comparison group experienced FNHTR. FNHTR was observed significantly lower (OR=29.4; CI=5.72–100) in the intervention group ($p<0.05$). To conclude, use of bedside leucodepletion filter significantly decreased the febrile nonhemolytic transfusion reactions in multi-transfused thalassemia patients.

Keywords: Thalassemia, Blood transfusion, Transfusion reaction, FNHTR, Leucodepletion filter.

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INTRODUCTION

Thalassemia is a blood disorder in which an abnormal form of hemoglobin is made due to genetic aberration.¹ Approximately 5000 children are born with thalassemia each year in Bangladesh.² Blood transfusion is the prime therapy for thalassemia major but is a double-edged sword with substantial cumulative risks including transfusion reactions, alloimmunization, and transfusion transmitted infections.³ Now-a-days thalassemia is a major health care challenge in Bangladesh and the largest consumer of its transfusion services. It is reported that 3% of the total blood is collected is spent on thalassemia patients.² Blood is an expensive and limited resource. Since it can save lives, it also leads to a number of adverse reactions in the recipients. Adverse reactions are an undesirable effect in a patient linked with the administration of blood or blood products.³ Half a century ago only whole blood was used for transfusion. However, now-a-days, whole blood has been separated into its various components such as RBCs, platelets and plasma.⁴ The average amount of leucocytes present in donated human blood is estimated to be 109/unit.¹ Until recently, little attention had been paid to the leucocytes present in various blood components. However, it has been shown that removal of leucocytes can minimize the risk associated with these contaminating leucocytes such as febrile nonhemolytic transfusion reactions (FNHTR), HLA alloimmunization, platelet refractoriness.^{1,5-7}

Thalassemia major patients are dependent on regular transfusion to sustain life. Multi transfuse thalassemia patients are prone to transfusion related complications. A common adverse effect of chronic transfusion in these patients is FNHTR with an occurrence rate of about 0.5-6.8% of all units transfused.⁵ The FNHTR occur due to immune reaction of the recipient's against donor leucocytes. FNHTR typically occur during transfusion but may arise within 4 to 6 hours after the transfusion has been completely administered. Most FNHTR are self-limited; characterized by fever ($>100.4^{\circ}\text{F}$ or 38°C), chills and rigors. Nausea, vomiting, dyspnoea, and hypotension may accompany these reactions.^{3,5,6} These reactions are generally not life threatening, but they are expensive in their management, evaluation, associated blood product wastage.⁵ FNHTR are results from leucocytes in transfused blood, destroyed by antibodies in the recipient, generating pyrogen

in vivo or by pyrogenic cytokines such as IL-6, IL-8, TNF- α , which are released during storage by contaminating leucocytes and platelets. In a multivalent analysis, the storage duration of RBCs before transfusion was identified as a more significant factor associated with FNHTR than leucocyte contamination.^{6,7} However, the ideal product for transfusion in thalassemia is packed red cells, preferably leucodepleted. According to the guidelines, the total amount of leucocyte present in a blood unit should be $<5 \times 10^6/\text{unit}$.² Leucodepletion is a process of removing leucocytes from the donated blood either during collection, processing or at the bedside.¹ There are several methods of leucodepletion of blood such as manual and automated cell washing, freezing and de-glycerolization of red cells, centrifugation and buffy coat removal, at bed side through leucocyte filters and blood component collection through apheresis technology. Currently the best leucoreduction can be achieved with the help of 3rd and 4th generation filters.⁷ Evidence showed that leucoreduction reduces the incidence of FNHTR and associated clinical costs significantly.⁵ Moreover, it is the prime responsibility of the physicians and the hospitals to offer their patients adequate and uninterrupted supply of the safest possible blood for transfusion when needed.⁸ Initially transfusion was given to these children only as a life saving measure but the patients suffered due to poor quality of life and remain incapacitated.⁹ With the availability of better transfusion regimen, iron chelation therapy, proper management complications and good supportive care, it is now possible for thalassaemic child to have a near normal life span with a good quality of life.¹⁰ Hence, in this study, we tried to compare adverse outcomes between two groups of thalassemia patients – transfused with packed red blood cells through conventional blood filter vs. transfused with leucodepleted blood using leucodepletion filter.

METHODS

This quasi-experimental study was carried out in the Department of Transfusion Medicine of Bangabandhu Sheikh Mujib Medical University (BSMMU), Dhaka, Bangladesh, between March 2019 and August 2021. A total of 84 diagnosed and transfusion dependent thalassemia patients were included in this study after fulfilling the eligibility criteria. They were equally divided into intervention and comparison group.

Inclusion criteria:

1. Thalassemia patient who are transfusion dependent; and
2. Patients who had subsequent two episodes of fever of at least 38°C or onset of chills and rigors within 24 hours of transfusion in a previously afebrile child (based on patient's history).

Exclusion criteria:

1. Multi-transfuse patients other than thalassemia and chronic anaemia;
2. Thalassemia patients suspicious of hemolytic transfusion reactions (based on clinical history and Coombs test report); and
3. Thalassemia patients suspicious of transfusion-associated sepsis (based on clinical history and physical examination).

We adopted a purposive sampling method. Selected patients were transfused by packed red blood cells and divided into two groups according to the status of leucodepletion method. Allocation of interventions were done by non-randomized alternate assignment. In this study, odd-numbered patients were transfused with packed red blood cells using leucodepleted filter (intervention group). On the other hand, the even numbered thalassemia patients were transfused with packed red blood cells with conventional blood transfusion filter (comparison group). Intervention and comparison groups were matched according to age, number of total transfusions, and previous history of febrile reactions. The temperature, pulse, blood pressure, and presence of any skin rash were recorded carefully before, during and after transfusions (within 1 hour). A semi-structured questionnaire was used to collect sociodemographic data, clinical history, investigations and transfusion related information of the participants. Data was also collected over mobile phone from those who developed reactions after being discharged from the hospital.

Data was collected, coded and compiled into the computer. Statistical Package for Social Sciences (SPSS) version 22.0 for Windows was used for statistical analysis. Unpaired Student's t-test was used to compare numerical data, while Chi-square test was used to compare categorical data. The level of significance was set at 5% and p-value <0.05 was considered statistically significant. Odds ratio with 95% CI were calculated for risk factor analysis.

RESULTS

The mean age was 19.11±16.54 years in intervention group and 15.79±10.83 years in comparison group. More than half (59.5%) of the patients were female in the intervention group and 23(54.8%) in the comparison group. More than one third (40.5%) of the patients were male in the intervention group and 19(45.2%) in the comparison group. Mean age was almost similar between two groups (p>0.05) (Table-I). Among adverse reactions, 21(25%) of the patients experienced chills and rigors - 2(4.8%) in the intervention group and 19(45.2%) in the comparison group. Other symptoms were only observed in the comparison group such as fever (38.1%), vomiting (4.8%), myalgia (7.1%), hypotension (2.4%) and skin rash (2.4%) (Table-II). Only 2(4.8%) patients had FNHTR in intervention group, while 25(59.5%) in comparison group experienced FNHTR. FNHTR was observed significantly lower (OR=29.4; CI=5.72-100) in the intervention group (p<0.05) (Table-III). We observed that only 1(50%) and 19(76%) patients had onset of reaction within 2 hours of transfusion in the intervention group and comparison group respectively. However, only 1(50%) and 6(24%) patients had onset of reaction after 2 hours of transfusion in the intervention group and comparison group respectively. The mean onset of reaction was 3.00±1.41 hours in intervention group and 3.07±2.62 hours in comparison group. The mean onset of reaction was similar between two groups (p>0.05) (Table-IV).

Table-I: Age and gender distribution of the study participants (N=84)

Variables	Intervention group (n=42)	Comparison Group (n=42)	p-value
Age group (in years)			
≤10	17 (40.5%)	15 (35.7%)	>0.05 ^{NS}
11-20	14 (33.3%)	19 (45.2%)	
21-30	4 (9.5%)	3 (7.2%)	
>30	7 (16.7%)	5 (11.9%)	
MeanSD (Range)	19.11±16.54 (4-64)	15.79±10.83 (4-60)	>0.05 ^{NS}
Gender			
Male	17 (40.5%)	19 (45.2%)	>0.05 ^{NS}
Female	25 (59.5%)	23 (54.8%)	

Unpaired Student's t-test and Chi-square test were applied respectively; NS=not significant .

Table-II: Transfusion related adverse reactions among the study participants (N=84)

Variables	Intervention Group (n=42)	Comparison group (n=42)
Fever	-	16 (38.1%)
Chills and rigors	2 (4.8%)	19 (45.2%)
Vomiting	-	2 (4.8%)
Myalgia	-	3 (7.1%)
Hypotension	-	1 (2.4%)
Skin rash	-	1 (2.4%)

Table-III: Comparison of febrile nonhemolytic transfusion reactions (FNHTR) between groups (N=84)

FNHTR	Intervention group (n=42)	Comparison Group (n=42)	Test statistics
Yes	2 (4.8%)	25 (59.5%)	$p < 0.05^S$
No	40 (95.2%)	17 (40.5%)	OR=29.4; CI=5.72-100

Chi-square test was applied; S=significant.

Table-IV: Comparison of the onset of reaction between groups (N=27)

Onset of reaction	Intervention group (n=2)	Comparison Group (n=25)	p-value
≤2 hours	1 (50.0%)	19 (76.0%)	
>2 hours	1 (50.0%)	6 (24.0%)	
Mean±SD (Range)	3.00±1.41 (1-4)	3.07±2.62 (1-10)	$> 0.05^{NS}$

Unpaired Student's t-test was applied; NS=not significant.

DISCUSSION

Febrile non hemolytic transfusion reactions (FNHTR) are the most common transfusion reaction among multi-transfuse thalassemia patient which is due to leukocytes contaminations in blood components. Though FNHTR is not life-threatening but it hampers their quality of life greatly. Sometimes transfusions have to be discontinued due to severity of febrile reactions with chills and rigors.^{7,9} In this study, we evaluated the effectiveness of using bedside leucodepletion filter for blood transfusion among thalassemia patient in reducing FNHTR.

In this present study, it was observed that 40.5% of patients belonged to age d"10 years in intervention group and 45.2% patients belonged to age 11–20 years in comparison group. The mean age was 19.11±16.54 years (ranged between 4 and 64 years) in intervention group and 15.79±10.83 years (ranged between 4.3 and 60 years) in comparison group. The mean age were almost similar between two groups. Tan et al. reported that the median age of the patients was 8 years, as they enrolled 26 multi-transfused thalassemic children aged between 9 months and 13 years, which is much less than that of our study because they they took only younger, pediatric patients in their study.⁹ In our study, females were predominant in both groups, i.e., 59.5% and 54.8% in intervention group and comparison group respectively. However, gender distribution was similar between two groups. Abdulqader et al. studied on 204 thalassemia major patients where 52% were male and 48% were female; no significant association was observed with gender, which is in congruence with the present study.¹¹

In the present study, 21(25%) of the patients experienced chills and rigors; 2(4.8%) in the intervention group and 19(45.2%) in the comparison group. Other symptoms were only observed in the comparison group such as fever (38.1%), vomiting (4.8%), myalgia (7.1%), hypotension (2.4%) and skin rash (2.4%). Waheed et al. observed febrile non hemolytic transfusion reaction (FNHTR) in 13.08% patients in the intervention groups. The clinical signs and symptoms of FNHTR were chills (51.1%), rigors (47.0%), fever (33.3%), hypotension (11.4%), vomiting (8.41%), myalgia (4.71%) and cough (3.0%).³ Abdulqader et al. observed 28% of patients had FNHTR manifested as fever and chills.¹¹ Most of the FNHTRs are self-limiting in nature; they are characterized by fever with or without chills and rigors. Nausea, vomiting, dyspnea, and hypotension may accompany these reactions.¹²⁻¹⁴ According to King et al., patients with a history of FNHTR are at a 15% risk of recurrence of such adverse reactions during subsequent transfusion.⁵ Tan et al. also reported that severe reactions (e.g., hemolytic transfusion reactions) were rare in their study, however, mild reactions (e.g., fever, urticaria and petechial rash) were common.⁹

In this study, we observed that 4.8% of patients had FNHTR in intervention group and 59.5% in comparison group. In a study done by Nasir et al.

study, reaction rate declined to 0%, when bedside filter was used and no FNHTR was documented on cases which had earlier reported high incidence of FNHTR.¹ On the other hand, use of non-leucoreduced blood resulted in the occurrence of febrile non-haemolytic transfusion reactions in 100% cases. Therefore, a remarkable reduction of FNHTR happened when a bedside filter leucoreduced blood is used compared to non-leucoreduced blood.¹ Devi & Gaikhonlungpou reported that transfusion reaction rate was observed 0.22% when leucoreduced blood was used and 0.58% when non-leucoreduced blood was used.¹⁴ However, Dutt et al. reported only 1 patient (0.8%) had such adverse event while receiving bedside filtered PRBCs, which is comparable to our study finding.¹⁵ In present study, in patients with bedside leucodepletion filters FNHTR significantly decreased 29.4 times compared to patients without leucodepletion filter ($p < 0.05$). Similarly, several previous studies reported that transfusion reactions were significantly reduced in the group receiving filtered blood.^{5,9,14-16} Comparing our study with the above mentioned studies, all got a similar domino effect highlighting that bedside leucodepletion filter is beneficial in reducing the incidence of FNHTRs. Anecdotal evidence may claim that bedside filter has no effect on reducing the rates of FNHTR; however, that could invariably happen in those centers, where filters used are invariable of sub-standard. Overall, leucoreduction using leucodepletion filter in thalassaemia patients helps us prevent transfusion reactions.

In this study, only 1(50%) patient had onset of adverse reaction >2 hours in intervention group and 76% in comparison group. The mean onset of reaction was 3 ± 1.41 hours in intervention group and 3.07 ± 2.62 hours in comparison group. The mean onset of reaction was similar between two groups. Tan et al. showed the median onset was 2 hours (ranged between 10 minutes and 18 hours), which is comparable with the current study.⁹

Our study had a relatively small sample and was done in a single hospital in Dhaka city due to time and budget constraint. Further studies can be undertaken with a large number of patients from different hospitals across the country under a randomized controlled trial.

CONCLUSION

It can be concluded that febrile non hemolytic transfusion reactions (FNHTR) were significantly reduced among those thalassemia patients who were transfused with packed red blood cells using leucodepletion filters. Adoption of this newer technology in multi-transfused patients like thalassemia can facilitate in minimizing the sufferings and thereby improving the quality of life. However, standard policy should be developed by the health authority to provide low-cost leukocyte free red cells in prospective recipients of multiple transfusions.

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Ethical approval: Ethical approval was obtained from the Institutional Review Board of Bangabandhu Sheikh Mujib Medical University (BSMMU), Dhaka, Bangladesh.

Authors' contribution: Conceptualization and design of the study: AA Urmi, A Khatun; patient selection, data collection and compilation: AA Urmi, UM Akter, AHMS Rahman, T Chakrabarty, R Yasmin; data analysis: AA Urmi, AM Appolo, MM Alam; supervision of the study: A Khatun; manuscript preparation, editing and final submission: AA Urmi, A Khatun, UM Akter, AHMS Rahman, T Chakrabarty, R Yasmin, AM Appolo, MM Alam.

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