Original Article

Effects of Prestorage Leukoreduction on the Rate of Febrile Nonhemolytic Transfusion Reactions to Red Blood Cells in a Tertiary Care Hospital

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Abstract

Background: Febrile nonhemolytic transfusion reactions (FNHTRs) are relatively common complications associated with allogenic transfusion. White blood cells (WBCs or leukocytes) are considered to be an important cause of FNHTRs; the rate of WBC derived pro-inflammatory cytokines increase with storage due to active synthesis of cytokines by these cells. The removal of the WBCs before storage will prevent the accumulation of cytokines during storage that leads to a reduction in the number of FNHTRs. **Aim:** We have conducted a retrospective analysis comparing the rate of FNHTRs in prestorage leukoreduced (PrSLR) and non leukoreduced RBCs transfusion. **Subjects and Methods:** A retrospective review of all the transfusion reactions (TRs) reported to the department over a period of 2 years from July 2012 to June 2014 was done. Patients were stratified by the date of reaction and by component received and then divided into two groups: (1) Patients who received allogeneic PrSLR RBCs and (2) nonleukoreduced RBCs. For the PrSLR RBC units, leukoreduction was performed by using buffy coat method of component preparation by quadruple bags and integral bags containing Sepacell® Pure RC filters (Fenwal™ France). **Results:** 37,232 RBCs units were transfused and out of which 14149 (38% i.e. is 14149/37232) were prestorage leukoreduced (PrSLR) and 23083 (62%) were non leukoreduced. A total of 142 (0.38%) TRs were reported during that time period, of which 62 (0.17%) were classified as FNHTRs. In the nonleukoreduced group 124 TRs were reported, of which 55 were classified as FNHTRs to RBCs and the overall rate of FNHTR to RBCs was 0.24%. In pre storage leukoreduced group, 18 TRs were reported, of which 7 were classified as FNHTRs to RBCs and the overall rate of FNHTR to RBCs was 0.05% ($P \leq 0.001$). This represents a significant reduction in the rate of FNHTR after institution of prestorage leukoreduction. **Conclusion:** The rate of FNHTRs to allogenic RBC units after the implementation of prestorage leukoreduction has decreased significantly. Cytokines and chemokines accumulating during storage of cellular blood products are responsible for residual FNHTRs.

Keywords: Febrile nonhemolytic transfusion reaction, Leukoreduction, Transfusion reactions

Introduction

Febrile nonhemolytic transfusion reactions (FNHTRs) are common complications resulting after transfusion of allogenic RBCs. Although they typically occur during the time of transfusion, these reactions may arise within 4–6 h after the transfusion. The frequency of febrile reactions in nonleukoreduced RBCs has been estimated to be 0.5–6.8% of all units transfused.[1,2] Patients with a history of FNHTRs are at a 15% risk of recurrence of this type of reaction.[3] Most FNHTRs are self-limited; they are characterized by fever (>1°C), chills and rigors. Nausea, vomiting, dyspnea, and hypotension may accompany these reactions, although they are not considered to be life threatening.[1]

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White blood cells (WBCs or leukocytes) are considered to be an important cause of FNHTRs; the rate of WBC derived pro-inflammatory cytokines increase with storage due to active synthesis of cytokines by these cells.[4] The interaction between the recipient's cytoxic antibodies and human leukocyte

antigen (HLA) or WBC-specific antigens located on donor WBC's, results in formation of antigen-antibody complexes leading to complement binding and release of endogenous pyrogens.[5] The removal of the WBCs before storage will both prevent the accumulation of cytokines during storage and will also remove the antigenic targets for preformed anti-WBC, leading to a reduction in the number of FNHTRs.[6] Despite the lack of change in cytokine levels during storage, prestorage leukoreduced (PrSLR) RBCs have been associated with lower rates of FNHTR compared to poststorage leukoreduced RBC units.[7,8] Poststorage WBC reduction has been shown to be equally effective in removing WBCs compared to prestorage WBC reduction and may even have added benefit of removing certain activated complement fragments, although it cannot abrogate the accumulation of WBC-derived cytokines during storage.[5]

Leukoreduced blood units were shown to minimize FNHTRs, HLA alloimmunization, platelet refractoriness and also prevent the transmission of leucotropic viruses such as cytomegalo virus (CMV), human T cell leukemia virus, and Ebstein bar virus.[9] Over the last 2 years, we have been gradually increasing our inventory of PrSLR RBCs, therefore we have conducted a retrospective analysis comparing the rate of FNHTRs in PrSLR and non leukoreduced RBCs transfusion in a tertiary care hospital.

Subjects and Methods

Study design

A retrospective review of all the transfusion reactions (TRs) reported to Department of Immunohematology and blood transfusion over a period of 2 years from July 2012 to June 2014 was done. Patients were stratified by the date of reaction and by component received and divided into two groups: (1) Patients who received allogeneic PrSLR RBCs and (2) allogeneic non leukoreduced RBCs. All RBC units, both leukoreduced and non leukoreduced were prepared in our component laboratory. For the PrSLR RBC units, leukoreduction was performed by using buffy coat method of component preparation by quadruple bags and integral bags containing Sepacell® Pure RC filter (Manufactured in France by Fenwal™ France and imported and marketed in India by Fenwal™ India, lot no 12G16 L02). Nonleukoreduced RBCs contain >10^9 WBCs. Leukoreduction by centrifugation and removal of buffy coat depleted RBCs give a log1 reduction (70–80%) of leukocytes in the unit (<5 × 10^8). Prestorage leukoreduction by Fenwal disposal: Sepacell® Pure RC filter from ASAHI produce a 2–4 log reduction (99–99.9%) of the WBCs (<5 × 10^6). Patients were not stratified on the basis of diagnosis, by inpatient or out-patient status at the time of the reaction. All data was categorized on a monthly basis. Reactions rates were calculated by dividing the number of reactions to each type of RBCs component by the total number of RBCs of that type transfused.

Evaluation of transfusion reactions

A standard TR investigation protocol was followed: All recognized TRs were reported to the blood bank on a standard reporting form. The clinical information included the patient's pre and post transfusion vital signs and other symptoms noted during the reaction. Further consultation with the ward, staff, patient and chart reviews was performed to resolve ambiguities. The remaining blood component and a post transfusion blood sample from the patient was sent to the blood bank where a clerical check was performed in parallel with a DAT on the post transfusion sample. Visual inspection of the plasma component of the post transfusion sample was performed for evidence of hemolysis. At the discretion of the blood bank consultant, bacterial cultures of the remaining segments, bag, and patient may be performed. Once the investigation was complete, results were reviewed. Reactions were classified in accordance with the standards and recognized definitions by American association of blood banks.[10]

Statistics

Statistical analyses SPSS for Windows version 20.0 (SPSS iNC., Chicago, IL, USA). of the rates of FNHTRs to different types of RBC products were compared using the Chi-square test.

Results

During the study period spanning 2 years, 37,232 RBCs units were transfused. Out of which 14149 (38% i.e. is 14149/37232) were pre storage leukoreduced and 23083 (62%) were non leukoreduced. A total of 142 (0.38%) TRs were reported during that time period, of which 62 (0.17%) were classified as FNHTRs. In the nonleukoreduced group 124 TRs were reported, of which 55 were classified as FNHTRs to RBCs and the overall rate of FNHTR to RBCs was 0.24%. In prestorage leukoreduced (PrSLR) group, 18 TRs were reported, of which 7 were classified as FNHTRs to RBCs and the overall rate of FNHTR to RBCs was 0.05% ($P \leq 0.001$) [Table 1]. This represents a significant reduction in the rate of FNHTR after institution of prestorage leukoreduction.

Discussion

Over the past 2 years, our department has gradually increased

Table 1: Comparison of FNTHRs between PrSLR and nonleukoreduced RBCs and number of transfusion reactions

Transfusion and reaction rate	PrSLR RBCs	Nonleukoreduced RBCs
Total RBCs transfusion	14,149	23,083
Total TR	18	124
FNHTRs	7	55
Rate FNHTRs	0.05	0.24
TRs (%)	0.13	0.54

PrSLR: Prestorage-leukoreduced, RBC: Red blood cell, FNHTRs: Febrile nonhemolytic transfusion reactions, TR: Transfusion reaction

the inventory of leukoreduced RBCs with a final goal of achieving leukoreduced RBCs transfusion with time. We had a policy of selective leukoreduced tranfusion for patients of thalassemia and for those who had previously experienced a FNHTR but gradually oncology and multitransfused patients were also included. There is a controversy in literature about the acute efficacy of leukoreduced RBCs in reducing FNHTRs.[11,12] Therefore we performed this retrospective study to assess the rate of TRs in patients who received PrSLR and non leukoreduced RBCs. Our transfusion service has a very aggressive and comprehensive method for the surveillance of TRs; it has an excellent rapport with other clinical services and has residents for immediate follow-up and evaluation as soon as TRs are reported.

In the present study, the incidence of TRs was found to be 0.38% in total, whereas in similar studies by University of Puerto Rico, Auckland Regional Blood centre and North India, who reported an incidence of 0.2%, 0.34%, 0.18% and 0.05% respectively.[13-16] The overall rate of TRs with non leukoreduced RBCs was 0.54% which is comparable with those reported in the literature for nonleukoreduced RBCs.[1,3,17] Our rate of TR in PrSLR RBCs was 0.13% and in a similar study by King *et al*.[18] Yazer *et al*.[19] and Shanthala Devi,[17] the rates of TRs were 0.40%, 0.69% and 0.26%.

We found a significant difference in the incidence of FNHTRs, that is, 0.05% versus 0.24% in PrSLR and nonleukoreduced RBCs. Several recent clinical trials have confirmed that prestorage leukocyte reduction is effective in reducing the rate of FNHTRs to red cells by approximately 50% with residual rates well below 1% [Table 2].[18-20] Serinolli *et al*.[21] reported a prospective trial in which the rate of FNHTR to nonleukoreduced RBCs (55/1521, 3.6%) was significantly higher than the rate of FNHTR to leukoreduced RBCs (13/1354, 1.0%).

The frequency of FNHTRs varies but with the use of leuco-reduced RBCs, the overall risk of FNHTRs has reduced to 0.24% in nonleukoreduced versus 0.05% in leukoreduced RBCs.[22] According to Sharma *et al*.[9] McNamara *et al*.[23] and Shapiro *et al*.[24] leukoreduction decreases the incidence of adverse effect of leucocytes in RBCs. In our study, the frequency of FNHTRs has been found to be consistently low, though increasing awareness and reporting about adverse reaction through hemovigilance system is balanced by the use of leukoreduced RBCs. There are a lot of variations in the frequency of FNHTRs among different studies throughout the world. This can be attributed to the variations in reporting system, frequent use of antipyretics and antihistaminics, and pretransfusion condition of the patient. This study has limitation because reaction rates were calculated from a retrospective review of passively reported reactions, under reporting of reaction could have lead to lower calculated rate of reactions and this can be improved by hemovigilance system. Leukoreduction has been particularly indicated in immunosuppressed patients who have an increased risk of transfusion-acquired CMV infection. These high risk recipients include: Low birth weight infants, oncology patients, and allogenic bone marrow recipients. The transfusion of blood from CMV sero-negative and leukoreduced blood components to these patients has shown to decrease the risk to 1.3%[17] and 2.5%[25] respectively. Over the last two decades, major trails have clearly shown that the relative risk of HLA alloimmunization can be reduced considerably through the use of leukoreduced blood products.[26]

Table 2: Comparison of FNHTRs in PrSLR and nonleukoreduced RBCs in various studies

Author	PrSLR RBC %	Nonleukoreduced RBCs %
Bhattacharya *et al*.[15]	0.19	0.33
Kumar *et al*.[16]	0.18	0.34
Shantala Devi and Gaikhonlungpou[17]	0.19	0.37
Present study	0.05	0.24

PrSLR: Prestorage-leukoreduced, RBC: Red blood cell, FNHTRs: Febrile nonhemolytic transfusion reactions

Conclusion

In conclusion our study demonstrated a significant decrease in the rate of FNHTRs to RBC units after the implementation of prestorage leukoreduction but cytokines and chemokines accumulating during storage of cellular blood products are responsible for residual FNHTR The questions of cost effectiveness and clinical relevance remain unanswered and will likely continue to be so until the other potential benefits of prestorage leukocyte reduction have been more fully elucidated. The reduction of FNHTRs is one of several arguments supporting the use of prestorage leukoreduction of RBCs and has a legitimate role to play in clinical transfusion practice. Patients who are multiple transfused, especially thalassemia major that have lifelong transfusion requirement, have the maximum benefit from such leukoreduced RBCs.

Limitation

Clinical reporting was the only source of information about incidence of transfusion reactions, thus the accurate figure for transfusion reactions was difficult to obtain.

Implication of using retrospective data helped us to collect large sample size which can help us in calculating the incidence of reaction rates and helps in framing the policies to reduce the reaction rate.

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