Original Article

Access this article online

Quick Response Code:

Website: www.ajts.org

DOI: 10.4103/ajts.ajts_90_22

Impact of buffy coat reduction on the severity of febrile nonhemolytic transfusion reactions with red cell components

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Abstract:

BACKGROUND: Febrile nonhemolytic transfusion reactions (FNHTRs) are the most common adverse reaction reported under the Haemovigilance Programme of India, and the use of leukodepleted blood products is recommended. The severity of the reaction may affect the morbidity associated with the reaction. This study aims to calculate the incidence of various transfusion reactions in our blood center and to evaluate the impact of buffy coat reduction on the severity of febrile reaction and other hospital resource-consuming activities.

MATERIALS AND METHODS: It was an observational retrospective study in which all reported FNHTRs were evaluated during the period July 1, 2018–July 31, 2019. Patient demographic details, component transfused, and clinical presentation were analyzed to identify factors affecting the severity of FNHTRs.

RESULTS: The incidence of transfusion reaction in our study period was 0.11%. Out of total 76 reactions reported, 34 (44.7%) were febrile reactions. Other reactions included allergic reactions (36.8%), pulmonary reactions (9.2%), transfusion-associated hypotension (3.9%), and others (2.7%). The incidence of FNHTR in buffy coat-depleted packed red blood cells (PRBCs) and PRBCs is 0.03% and 0.05%, respectively. FNHTRs are seen more in females with prior history of transfusion (87.5%) as compared to males (66.67%) ($P = 0.046$). We also found that FNHTRs are less severe with buffy coat-depleted PRBC transfusion than PRBC transfusion as mean ± standard deviation temperature rise was less in buffy coat-depleted PRBC (1.3 ± 0.8) than PRBC (1.74 ± 1.129). The febrile response to buffy coat-depleted PRBC transfusion occurred at higher volume (145 ml) transfusion than PRBC transfusion (87.2 ml), and it was statistically significant ($P = 0.047$).

CONCLUSION AND SUMMARY: Leukoreduction remains the main modality to prevent FNHTR, but in developing countries like India, the use of buffy coat-depleted PRBC over PRBC can reduce the incidence and severity of FNHTR.

Keywords:

Direct antiglobulin test, febrile nonhemolytic transfusion reaction, Haemovigilance Programme of India, International Society of Blood Transfusion, packed red blood cells, SAGM packed red blood cells, tumor necrosis factor

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Submitted: 11-07-2022
Revised: 21-08-2022
Accepted: 11-09-2022
Published: 12-12-2022

Introduction

According to the International Society of Blood Transfusion, febrile nonhemolytic transfusion reaction (FNHTR) is characterized by a posttransfusion rise of more than 1°C or chills and rigor unrelated to the underlying condition.[1] It may be accompanied by nausea and headache occurring within 4 h of transfusion ruling out hemolytic transfusion reaction, bacterial contamination, and any other cause.[1] It

How to cite this article: Singh L, Prinja N, Jain A, Sharma RR, Marwaha N. Impact of buffy coat reduction on the severity of febrile nonhemolytic transfusion reactions with red cell components. Asian J Transfus Sci 2023;17:69-73.

occurs either due to the interaction of antibodies in patient plasma with donor leukocytes or from inflammatory mediators released by the leukocytes produced during storage.[2] In immune-mediated febrile reactions, leukocyte antibodies are formed in recipients due to transfusion, pregnancy, or any other event and interact with leucocytes in transfused blood components which results in the release of pyrogens such as interleukins and tumor necrosis factor resulting in FNHTR.[3] The storage of cellular components such as platelets and red cells leads to the accumulation of pro-inflammatory cytokines that may lead to FNHTR.[3] A lot of variation in the incidence of FNHTR has been seen due to blood product and patient-related variables including type, age, leukoreduction status of product, and antipyretic intake, respectively.[4] This is generally prevented by one log reduction of leukocytes in blood components or the use of single-donor blood components.[5] As per the report from the Haemovigilance Programme of India (HvPI), FNHTRs are the most common adverse reaction reported. It also recommends leukodepletion of blood products for the prevention of FNHTR's.[6] The severity of the reaction can vary from mild to moderate to severe. It causes discomfort to the patient. It can exacerbate underlying health conditions, hence transfusion should be stopped immediately,[7] and blood bank should be informed immediately for further workup. This study aims to calculate the incidence of various transfusion reactions in our blood center and to evaluate the impact of buffy coat reduction on the severity of febrile reaction and other hospital resource-consuming activities.

Materials and Methods

It was an observational retrospective study in which all the details of FNHTRs reported to the department of transfusion medicine from July 2018 to July 2019 were analyzed. Patient demographic details, type of component transfused, and posttransfusion clinical presentations were analyzed to identify various factors affecting the severity of FNHTRs. A compatibility report is provided with every blood component issue. The clinicians were asked to follow the bedside transfusion instructions, i.e. red cell transfusions to be transfused within 30 min of the issue and completed within 4 h and for platelet concentrate and fresh frozen plasma transfusion to be started at the earliest after the receipt of blood components at the patient bedside and to be completed in 20–30 min. Clinical residents from all the clinical specialties of our institute are trained for reporting data to the pretransfusion testing laboratory of our department. When adverse transfusion reaction is identified by a clinician/nursing officer, transfusion is stopped immediately. Then, it is informed telephonically to the doctor on call in transfusion services. Complete details of the transfusion reaction are recorded and sent to the pretransfusion testing laboratory along with the used component bag, blood transfusion set, and posttransfusion sample taken from the site other than the implicated for transfusion reaction. Reported reactions were evaluated. To rule out wrong sampling/bedside error, the patient's identification details such as name, age, sex, and hospital registration number are rechecked both on the pre- and posttransfusion sample vials and requisition form. A gross examination of blood bag and transfusion set was done for any discoloration, clot, and hemolysis. Any evidence for thermal injury was looked upon by inspecting the bedside storage conditions of blood component after it was released from the blood bank. Pre- and posttransfusion samples of the patient were checked for hemolysis. Results of blood typing were compared with the previous records if the patient was transfused previously. The reconfirmation of ABO and Rh typing of the patient and blood product was done with repeat compatibility testing on both the samples. Clinical signs and symptoms were evaluated. Investigations such as direct antiglobulin test and indirect antiglobulin test were done. A sample from blood bag was taken in a blood culture bottle for microbiological examination. Other details which include storage conditions between component issue and transfusion were also noted.

Flowchart 1: Flowchart for Reporting Adverse Transfusion Reactions

Adverse transfusion reaction observed by a bedside physician/nursing officer

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Informed telephonically to the department of transfusion medicine and documentation on compatibility report is done

↓

Blood bag with transfusion set, posttransfusion sample along with filled form, is sent to the department of transfusion medicine

↓

Other relevant investigations are sent to various laboratories from the ward

↓

Requisition form is checked for any clerical errors

↓

Further investigations such as repeat blood grouping – ABO and Rh (D), direct antiglobulin test,

cross-matching, and antibody screen are done with posttransfusion sample. Blood culture is sent to the microbiology laboratory

↓

Any further investigations required to diagnose the type of transfusion reaction are done

↓

Imputability of transfusion reaction is assessed in coordination with a clinical physician

↓

Reactions are reported to the national nodal center for hemovigilance

Results

A total of 52,289 PRBCs and 16,559 buffy coat-depleted PRBCs were distributed with an incidence of 0.11% transfusion reaction during our study period from July 2018 to July 2019. A total of 76 reactions were reported in our study period. Out of 76 reactions [Figure 1] reported, 34 (44.7%) were febrile reactions. Other adverse reactions reported were allergic reactions 28 (36.8%), followed by pulmonary reactions 7 (9.2%), transfusion-associated hypotension 3 (3.9%), hemolytic transfusion reactions (2.7%), and others (2.7%). Other reactions included transfusion-transmitted bacterial infection and transfusion-associated anxiety.

Thirty-four FNHTRs were reported in our study period. Eighteen reactions were reported in males and 16 were reported in females. The mean age of patients is of 40.71 years. Four patients had only chills and rigor with no increase in temperature. Twelve patients had a 1° rise in temperature and the rest of the patients presented with severe FNHTR (>2°C). Among the patients with severe FNHTR, 10, 5, and 3 patients had a 2°, 3°, and 4° rise in fever, respectively [Figure 2]. *Staphylococcus hominis* growth was seen in culture in one case. Among 34 FNHTRs, imputability in 24 reactions was probable, possible in 5 reactions, definite in 3 reactions, and unlikely in 2.

Out of the 34 reported febrile reactions, one was due to apheresis platelet transfusion and the remaining reactions were due to red cell transfusion. The incidence of FNHTR in buffy coat-depleted PRBC and PRBC is 0.03% and 0.05%, respectively. FNHTRs are seen more in females with prior history of transfusion (87.5%) as compared to males (66.67%) (P = 0.046). Eighty-five percent of total febrile reactions were due to PRBC transfusion (nonbuffy coat depleted) transfusion and approximately 12% were due to buffy coat-depleted PRBC transfusion. It is a known fact that the incidence of FNHTR decreases with buffy coat depletion and we observed the same in our study also. A decrease in the incidence of FNHTR decreases the need for other biochemical and microbiology tests and its associated cost. However, one interesting finding in our study is that the FNHTR is less severe with buffy coat-depleted PRBC transfusion than PRBC. Table 1 shows the characteristics of FNHTR with respect to the rise in temperature during the reaction, the volume of blood component transfused, and the time gap between initiation of transfusion and transfusion reaction.

It was found that the temperature rise was higher with PRBC transfusion [Figure 3]. Temperature rise with buffy coat-depleted PRBC was 1.3 ± 0.8 and PRBC was 1.74 ± 1.13. Although the results were not statistically significant, yet it implies that buffy coat depletion in

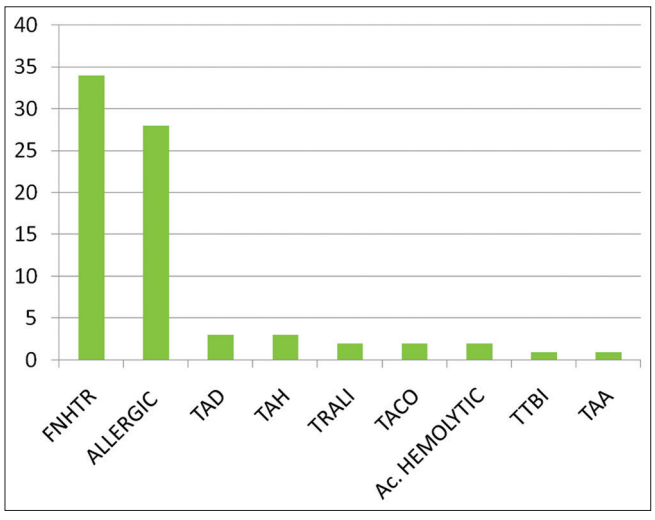

Figure 1: Incidence of various transfusion reactions in our study

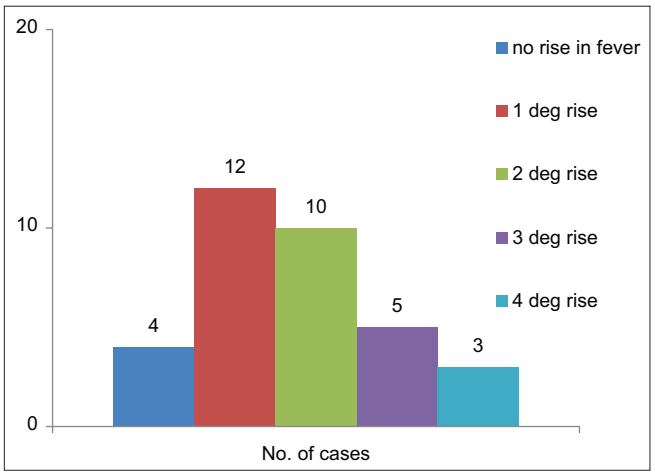

Figure 2: Rise in temperature in 34 cases of FNHTR. FNHTR: Febrile nonhemolytic transfusion reaction

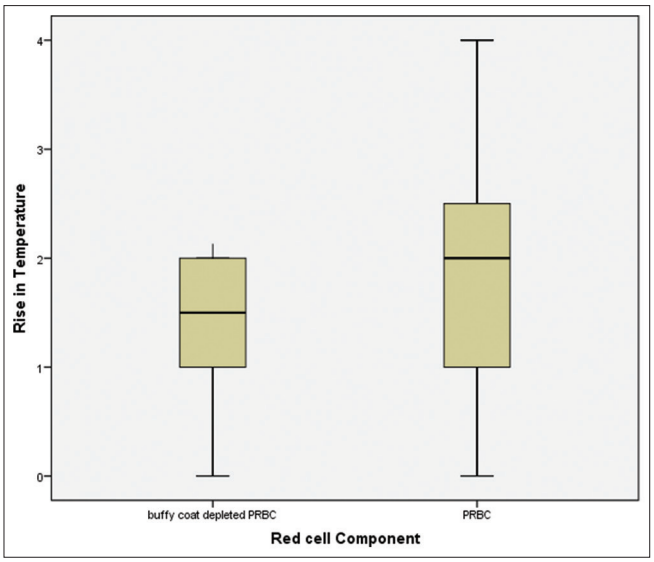

Figure 3: Box plot chart shows the mean ± SD rise in temperature in buffy coat depleted and PRBC transfusion. It highlights the higher increase in temperature in a patient receiving PRBC transfusion as compared to buffy coat-depleted PRBC transfusion. SD: Standard deviation, PRBC: Packed red blood cell

a certain group of patients may decrease the severity of febrile reaction in terms of rise in temperature. Thus Buffy coat depletion can help in preventing any sequelae to transfusion reaction in predisposed patients. The other concern with transfusion reactions is the inability to transfuse due to transfusion reaction as transfusion needs to be stopped immediately after transfusion to rule out any hemolytic cause of transfusion reaction. FNHTRs are generally benign reactions, but these blood units are discarded and it adds to the financial burden on the hospital. We found that febrile response to buffy coat-depleted PRBC transfusion occurred at higher mean volume (145 ml) transfusion than PRBC transfusion (87.2 ml), and this difference between PRBC and buffy coat-depleted PRBC was statistically significant. Furthermore, the transfusion reaction with buffy coat-depleted PRBC occurred later than PRBC transfusion, as shown in Table 1. The mean time gap between initiation of transfusion and transfusion reactions was 80 min and 115 min with PRBC and buffy coat-depleted PRBC, respectively. Hence, more red cell volume is transfused with more benefit to the patient and may help in the reduction of patient cost for the hospital authorities.

Discussion

This study was done from July 2018 to July 2019 in a tertiary care hospital. Transfusion of blood and blood components can sometimes lead to adverse events in the form of adverse transfusion reactions which are then reported online to form a national database. Coordination between the clinical and transfusion teams

Table 1: Characteristics of febrile nonhemolytic transfusion reactions with respect to rise in temperature during the reaction, the volume of blood component transfused, and the time gap between initiation of transfusion and transfusion reaction

	PRBC	Buffy coat-depleted PRBC	*P*
Mean±SD rise in temperature in degrees Celsius	1.74±1.13	1.3±0.8	0.16
Mean volume at which the transfusion reaction occurred	87.2	145	0.047
Meantime in a minute after which the transfusion reaction occurred	80	115	0.08

PRBC=Packed red blood cell, SD=Standard deviation

is of utmost importance for timely identification of events and hence its clinical management.

Total transfusion reactions reported in our study was 76 with an incidence of 110 transfusion reactions per lakh of red cell component transfused. The rate of occurrence of transfusion reaction in our study was less as compared to other studies in which the incidence varies from 0.18% to 0.42%.[8-11] FNHTRs constitute the highest percentage, followed by allergic reactions and other reactions. This correlated with other studies done by Bhattacharya *et al*.,[8] Chowdhury *et al*.,[12] Khalid *et al*.,[13] and Bassi *et al*.[14]

Eighty-five percent of FNHTR was due to PRBC transfusion (nonbuffy coat depleted) and the reason was that the components were not leukoreduced which results in the interaction of antibodies in a patient with antigens on donor leukocytes resulting in febrile reactions. In addition, the level of pro-inflammatory cytokines also increases in nonleukoreduced blood components during storage which can also lead to febrile reactions. Various studies have shown that the incidence of FNHTR to red cell transfusion can be decreased with universal leukoreduction. The incidence of FNHTR with nonleukoreduced red cell components and leukoreduced red cell components was 0.24% and 0.05%, respectively, as shown in a retrospective analysis from India.[15] In a study by King *et al*., the incidence of FNHTR due to red cell transfusion significantly decreased from 0.37% to 0.19% after the introduction of leukoreduction in their center.[3] Buffy coat removal has also been shown to be an effective intervention to reduce the incidence of FNHTR in thalassemic patients by Neeti *et al*. from India.[16] In our study, we found a single FNHTR in a female patient with apheresis platelets and that can be due to preformed leukocyte antibodies either due to prior transfusion or due to pregnancy.

Interesting findings we found in our study were that FNHTRs are less severe with buffy coat-depleted PRBC

transfusion than PRBC transfusion which was evident mainly from two factors, i.e. temperature and volume. Temperature rise (mean ± standard deviation) was less severe with buffy coat-depleted PRBC transfusion. The rise of temperature with buffy coat-depleted PRBC was 1.3 ± 0.8, and the rise of temperature with PRBC was 1.74 ± 1.129. Febrile response to buffy coat-depleted PRBC transfusion occurred at higher volume (145 ml) transfusion and later than PRBC transfusion (87.2 ml). Hence, we can say that no doubt leukoreduction is the main modality to prevent FNHTR, but in developing countries like India, the use of buffy coat-depleted PRBC over PRBC can reduce both incidence and severity of FNHTR.

Conclusion

Maximum number of transfusion reaction reported were FNHTR, followed by allergic reaction. Reporting every transfusion reaction is a must for medical education and strengthening of Indian hemovigilance system. In developing countries where universal leukoreduction is difficult to achieve, the use of buffy coat-depleted PRBC (SAGM-PRBC) over PRBC can reduce the intensity and severity of FNHTR.

Financial support and sponsorship
Nil.

Conflicts of interest
There are no conflicts of interest.

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