Study of acute transfusion reactions in a teaching hospital of Sikkim: A hemovigilance initiative

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ABSTRACT

Objective: Blood transfusions are inherently associated with risks ranging in severity from minor to life-threatening. Continuous monitoring of transfusion related complications can promote understanding of factors contributing to transfusion reactions and help to formulate necessary remedial measures. This study was designed to analyze the frequency and nature of transfusion reactions reported to the blood bank of a remote North East Indian teaching hospital.

Materials and Methods: All acute transfusion reactions (ATRs) reported to the blood bank over a period of 20 months (May 2013 to January 2015) were reviewed and analyzed. The risk of transfusion reactions associated with each individual component was assessed.

Results: A total of 3455 units of whole blood and component transfusions were carried out of which a total of 32 (0.92%) ATRs were encountered. Packed red blood cells (PRBCs) \( n = 15, P = 0.06 \) and whole blood (WB) \( n = 13, P = 0.83 \) were most commonly implicated. Allergic reaction was the most frequent transfusion reaction encountered (65.6%), seen most commonly with PRBC (risk of 0.76%, \( P = 0.42 \)), and WB (risk of 0.68%, \( P = 0.63 \)) transfusions. This was followed by febrile reactions (28.1%), which were seen more commonly with PRBCs (risk of 0.57%, \( P = 0.016 \)). No reactions were observed with platelet transfusions.

Conclusion: The overall incidence of transfusion reactions in this hospital is slightly higher than those having more advanced transfusion facilities in India. The lack of leukoreduction facilities in our hospital could be a likely cause for the same. The use of leukoreduced WB and PRBCs could possibly reduce the overall incidence of ATRs in general and febrile nonhemolytic transfusion reactions in particular.

KEY WORDS: Acute transfusion reactions, allergic reactions, febrile reactions, hemovigilance, transfusion related adverse events

Introduction

Access to adequate and safe blood transfusion facilities is integral to any basic health care delivery infrastructure. They are often lifesaving in critically ill patients. On the flipside, blood transfusions are also inherently embedded with risks ranging in severity from minor to life threatening.\(^1\) Judicious patient selection with pragmatic pretransfusion assessments of risk versus benefit to the potential recipient combined with stringent quality control is an effective mode of reducing transfusion related adverse events. In addition, continuous monitoring of transfusion related complications can promote patient care and safety. The goal of hemovigilance was to observe, identify,
and prevent the occurrence or recurrence of transfusion related unwanted events so as to increase the safety, efficacy, and efficiency of the blood transfusion process, covering the entire blood transfusion chain of donors to recipients. On the basis of this core principle, The Haemovigilance Programme of India (HvPI) was launched by the Indian Pharmacopoeia Commission in collaboration with the National Institute of Biologicals on December 10, 2012. The HvPI that comes under the Pharmacovigilance Programme of India (PvPI), tracks adverse reactions related to blood transfusions and blood product administration in affiliated blood banks across India. Our institute obtained approval for a component in the year 2011 and affiliation to the HvPI, in 2013.

This study was carried out with the objective of observing and analyzing the acute transfusion reactions (ATRs) encountered in the blood bank of this remote North Eastern teaching hospital. This workup would enable us to develop insight into ATR patterns not yet documented from remote centers like ours and compare them with that of larger national and international transfusion centers.

**Materials and Methods**

**Study Setting and Duration**

The study was conducted in the Department of Transfusion Medicine, (HvPI centre), and the Department of Pharmacology, (PvPI centre) of this North East Indian medical institute and attached teaching hospital. Approval for conducting the study was obtained from the Research Protocol Evaluation Committee and the Institutional Ethical Committee. This was a retrospective observational study in which all ATRs reported to the blood bank over a period of 20 months (May 2013 to January 2015) were reviewed and analyzed.

**Standard Procedure for Adverse Event Prevention, Detection, Evaluation, and Reporting**

The hospital is following the standard operating procedures adapted from the CDSCO technical manual for transfusion, starting with donor selection, phlebotomy, component processing, testing for infectious diseases, storage, cross matching, issue of component, and follow-up of the recipient. The paramedical staff involved in blood transfusion has been trained in transfusion practices, enabling them to identify and manage any encountered transfusion reaction at the earliest. Prior to the transfusion, they are required to cross-check for any clerical errors, ABO-Rh group of the patient and the blood bag, types of blood products and blood unit number, inspect the blood bag for hemolysis, clot and leakage, and expiry date. In the event of a transfusion reaction, the transfusion reaction form is being filled with information pertaining to: The date and time of initiation and cessation of the transfusion, time of the reaction, patients pre- and post-transfusion vital signs, approximate volume of blood transfused, as well as clinical signs and symptoms. The reaction form along with the posttransfusion blood sample (2 ml in citrate vial and 2 ml in plain vial), urine sample, and the leftover blood product bag, and transfusion set are immediately sent to the blood bank. The blood bank performs a thorough evaluation of the suspected transfusion reaction and rechecks the blood requisition form, returned blood/component unit number, ABO-Rh grouping and screening for irregular antibodies. Blood grouping of the patient is repeated and compared with the pretransfusion sample. The blood bag and attached transfusion set is inspected for hemolysis, discoloration, clot or leakage. Bacteriological testing of the bag and tubings is done by the microbiology department. Posttransfusion blood sample is checked for hemolysis and compared with the pretransfusion sample. In case of a suspected hemolytic reaction, further investigations done include:

- Qualitative and quantitative estimation of plasma hemoglobin %
- Direct antiglobulin test
- Hemoglobinuria: Gross visual examination and urine hemoglobin by dipsticks
- Hematuria: Microscopic examination
- Serum total and unconjugated bilirubin
- Peripheral blood smears examination for the presence of schistocytes and spherocytes.

Compatibility testing is repeated on pre- and post-transfusion sample: Diamed-ID Microtyping System. In case of a reaction such as transfusion-related acute lung injury (TRALI) and pulmonary embolism, chest X-ray report is cross checked. Based on the clinical features mentioned in the transfusion reaction form, and the laboratory reports, the reactions are classified according to the standard criteria defined by the American Association of Blood Banks. After completion of transfusion reaction workup and categorization of the transfusion reaction, data are submitted to the HvPI.

**Data Analysis**

The data collected for this study were analyzed for frequency, percentage, mean, and standard deviation. Statistical software used was Microsoft Office Excel 2007 and IBM SPSS Statistics version 20 (Statistical Package for the Social Sciences IBM Corporation).

The Chi-square test was used where applicable, and \( P < 0.05 \) was considered significant.

The following parameters were calculated and tabulated/depicted graphically.

1. Frequency of component/whole blood transfusions: \( \frac{NC}{NT} \times 100 \) where “NC” is the number of component/whole blood units transfused and “NT” is the total number of transfusion units [Table 1; Column 3]
2. Risk of transfusion reactions with a particular component/whole blood: \( \frac{NTRC}{NC} \times 100 \) where “NTRC” is the total number of reactions encountered with a particular component/whole blood, and “NC” is the total units of component/whole blood transfused [Table 1; Column 5]
3. Risk of a particular reaction with a particular component/whole blood: \( \frac{NPTR}{NC} \times 100 \) where “NPTR” is the total number of a particular transfusion reaction, and “NC” is the total number of components/whole blood units transfused [Table 2; Column 2, 3, and 4]
4. Frequency of a particular reaction in relation to total number of transfusions: \( \frac{NPTR}{NT} \times 100 \) where “NPTR” is the total number of the particular transfusion reaction and “NT” is the total number of transfusion units [Table 2; Column 5]
5. Frequency of particular reaction in relation to total
number of transfusion reactions: NPTR/NTR × 100 where “NPTR” is the total number of the particular transfusion reaction and “NTR” is the total number of transfusion reactions [Figure 1].

Results

A total of 3455 units of whole blood and component transfusions were carried out in the study duration, out of which a total of 32 (0.92%) ATRs were encountered. Table 3 depicts the demographic characteristics of the recipients reported with transfusion reactions. The age of the recipients ranged from 14 to 88 years, with the mean age of females (43.7 years) slightly lower than that of males (44.3 years). There was a female preponderance (59.4%) in the frequency of transfusion reactions, over males (40.6%). However, this difference was not significant ($P = 0.13, \chi^2 = 2.25$). Transfusion with packed red blood cell (PRBC) was most commonly associated with adverse reactions (15 reactions out of a total of 1042 transfusions; $P = 0.06, \chi^2 = 3.52$), followed by whole blood (WB) transfusions (13 reactions out of a total of 1467 transfusions; $P = 0.83, \chi^2 = 0.045$) [Table 1]. A total of 650 units of fresh frozen plasma (FFP) transfusions were carried out that finally resulted in four reactions ($P = 0.36, \chi^2 = 0.84$). No reactions were encountered with platelet, cryoprecipitate, and cryo poor plasma transfusions. Allergic reaction was the most frequently encountered transfusion reaction (65.6%) [Figure 1], which was most commonly seen with PRBCs (risk of 0.76%; $P = 0.42, \chi^2 = 0.63$) and WB (risk of 0.68%; $P = 0.63, \chi^2 = 0.23$) [Table 2]. This was followed by febrile nonhemolytic transfusion reactions (FNHTRs) (28.1%), which was seen more commonly with PRBCs (risk of 0.57%; $P = 0.016, \chi^2 = 5.7$). There was one reaction each of anaphylaxis and pulmonary embolism, following WB and PRBC transfusions, respectively. No hemolytic reactions were encountered in the study period.

The mean volume of blood at which transfusion reaction had occurred was 192.5 ± 95.7 ml [Table 4]. Figure 2 shows the relative frequency of transfusion reactions according to the department in which the recipients were being treated, and the adverse event reported. Most common manifestations included urticaria and itching ($n = 14$ each), followed by fever ($n = 9$), dyspnea ($n = 7$), and increased pulse rate ($n = 6$) [Figure 3]. Less frequent manifestations included hypotension, muscle aches, headache, and hypertension.

Discussion

The safety concept of hemovigilance had its inception in the early 1990s. The French blood agency had initially developed it as a national system of surveillance and alert, from blood collection to the follow-up of recipients. Hemovigilance is currently recognized as an indispensable component of quality management in blood programs globally. An ideal hemovigilance system is designed to detect, gather, and analyze unexpected or undesirable effects associated with transfusion. The information obtained is intended to bring about required changes in transfusion policies, improve transfusion standards, assist in the formulation of transfusion guidelines, and thus improve safety and quality of the transfusion process. It is thus not only an avenue to analyze blood transfusion incidents, but also a tool to measure the effects of new processes or corrective actions implemented to remedy their causes and prevent their recurrence. Noninfectious adverse transfusion reaction (NIATRs) such as acute hemolytic transfusion reactions, FNHTRs, anaphylactic reactions, TRALI, and allergic reactions are recognized as predominant contributing factors of transfusion-related morbidity and mortality. ATRs are those acute or nonimmune adverse reactions that occur within 24 h of the transfusion. The estimated frequency of ATRs varies from 0.2% to 10%, and mortality is approximately, 1 in 250,000.
In this study, the frequency of ATRs was observed to be 0.92%, which was comparable to that of a study carried out in Punjab, where the incidence of ATRs was 1.09%. Two larger studies done in New Delhi and Chandigarh, however, showed a relatively lower frequency of transfusion reactions (0.05% and 0.18%, respectively). A study in Switzerland and the Quebec hemovigilance system reported transfusion reaction rates of 0.042% and 0.035%, respectively. The incidence of transfusion reactions at our center was thus higher than that observed at some national and international centers.

The most common ATR observed was an allergic reaction (65.6% of all ATRs), which presented most commonly with urticaria and/or itching. There was no significant difference observed between the number of allergic reactions and type of transfusion ($P > 0.05$ for WB, PRBC, and FFP transfusions). Allergic reactions can occur in up to 2% of transfusions as a result of recipient IgE and donor antigen interactions triggering the release of histamine and de novo synthesis of leukotrienes and platelet activating factor. Clinically, allergic reactions have been discerned from the more severe anaphylactoid reactions by the absence of clinical manifestations such as bronchospasm and/or hypotension. Similar to the findings of this study, allergic reactions were also found to be the most common transfusion reaction in studies done in Delhi (55.1%) and Iran (49.2%). However, the overall incidence of allergic reactions in the study done in Delhi was only 0.02%, which was lower than the incidence of allergic reactions in our study (0.6%).

FNHTR, which is defined as an otherwise unexplained rise in temperature of at least 1°C during or shortly after transfusion, comprised of 28% of the total ATRs, in this study (0.26% of total transfusions). FNHTRs are reported to be more common with platelet transfusions than PRBCs because platelets require storage at 20–24°C, which results in donor leukocyte activation and pro-inflammatory cytokine accumulation. However, FNHTRs were found to be more with PRBCs (0.57% of all PRBC transfusions) and WB (0.13% of all WB transfusions) than platelets, with which no reactions were
The introduction of FNHTRs with transfusion of nonleukoreduced whole blood and PRBCs was estimated to be 0.114% in a study done in Chandigarh, which is closer to the incidence of FNHTRs (9,16) because acellular plasma components rather than leukocytes in blood components contribute to allergic ATRs. The introduction of leukoreduction at our institution could possibly enable us to reduce the incidence of ATRs in general and febrile reactions in particular.

There was one fatal transfusion event, in which a recipient suffering from deep vein thrombosis, developed severe respiratory distress, frothing from the mouth, collapsed, and eventually died. Postmortem findings ascertained pulmonary embolism, which was, however, confirmed as not being due to air emboli. Any direct causality with the transfusion process was thus ruled out.

**Conclusion**

The overall incidence of transfusion reactions in this hospital is slightly higher than those having more advanced transfusion facilities in India. There was no significant difference among the overall incidence of ATRs based on the type of component transfused. However, a significant association was observed between the number of PRBC transfusions and febrile reactions. The use of leukoreduced WB and PRBCs could possibly reduce the incidence of ATRs in general and FNHTRs in particular.

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**Conflicts of Interest**

There are no conflicts of interest.

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