

Acute blood transfusion reactions in a tertiary care hospital in Pakistan - an initiative towards haemovigilance

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SUMMARY

Objective: In this study, we report acute blood transfusion reactions at our hospital, compare our analysis with the reported data and identify areas for improvement.

Background: Haemovigilance programmes have been implemented in many countries, and adverse events associated with blood transfusion are published in their annual reports. Pakistan has no current established programme.

Material and Methods: A cross-sectional study was conducted, and all adverse reactions reported to the blood bank from January 2014 to March 2016 were included. An adverse response in the patient, related to administration of blood (within 24 h), was considered an immediate transfusion reaction.

Results: During the study period, 20 956 blood components were issued. A total of 32 (0.15%) adverse reactions were documented. Allergic reactions were the most common adverse event observed in 15 (46.8%) of the cases. Febrile non-haemolytic transfusion reaction (FNHTR) was the second most common reaction seen in nine (28%) followed by bacterial contamination in four (12.5%) and acute haemolytic reaction in two (6.2%) of the cases.

Conclusion: The low incidence indicates underreporting and the need for a formal haemovigilance system. International benchmarking between different medical systems is helpful to identify areas in the transfusion process that have to be changed to improve transfusion safety.

Key words:

Blood transfusion is an indispensable component of patient management. However, blood transfusion therapy may cause acute or delayed transfusion reactions (Sousa Neto

& Barbosa, 2011). A transfusion reaction is defined as any transfusion-related adverse event that occurs during or after the transfusion of blood or its components (Rathod *et al.*, 2016). Acute transfusion reactions (ATRs) occur during or within 24 h of transfusion and include acute haemolytic transfusion reaction (AHTR), allergic, febrile non-haemolytic transfusion reaction (FNHTR), fluid overload, transfusion-related acute lung injury (TRALI), anaphylactic and metabolic reactions (Khalid *et al.*, 2010; Sousa Neto & Barbosa, 2011).

Various countries like United Kingdom and France have developed and implemented haemovigilance programmes to systematically collect and report adverse events associated with blood transfusion (Khalid *et al.*, 2010; Sidhu *et al.*, 2015). No haemovigilance system has been established in Pakistan. At the same time, pre-transfusion laboratory investigations are less extensive in Pakistan compared to countries who can afford to invest more resources into their medical system, e.g. only ABO blood group system (ABO) and Rhesus D and not Rhesus C, c, E, e or Kell or Duffy are determined and matched for transfusion (Zaidi *et al.*, 2015). In the present study, we evaluated acute adverse transfusion reactions at our centre, estimated their frequency and compared it with previous data to identify areas for improvement as an initiative towards haemovigilance.

PATIENTS AND METHODS

This cross-sectional study was conducted at National Institute of Blood Disease And Bone Marrow Transplantation (NIBD), Karachi, Pakistan. The institutional ethics committee approved the study. Informed consent was obtained from all adult subjects, parents or legal guardians.

Blood products are issued only after serological testing for hepatitis B, C, HIV and syphilis along with thick smear evaluation for malaria. The blood bank policies and standard operating procedures (SOPs) are derived from the American Association of Blood Bank (AABB). The blood is not leuko-depleted; however, there is provision of bedside filters when requested. In the patient, ABO and Rh D blood type are determined, and red cell concentrates are cross-matched with the patient's serum using anti-human globulin. In this study, transfusion reactions

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reported to the blood bank over a period of 2 years (from January 2014 to March 2016) were analysed. When a transfusion reaction had been reported to the blood bank, a transfusion reaction form was provided to the medical staff, and details were noted. The form was sent back to the blood bank along with the blood bag and patient's blood and urine samples. Transfusion-related adverse reactions were scrutinised using a standard transfusion reaction investigation protocol, which included:

- 1 Clerical checks
- 2 Post-transfusion blood sample was inspected for any evidence of haemolysis and compared with a pre-transfusion sample, if available
- 3 Patient's pre- and post-transfusion sample, together with donor's sample, were rechecked for blood grouping.
- 4 Patient's pre- and post-transfusion samples were checked for direct and indirect anti globulin test (DAT).
- 5 Bacteriological culture
- 6 Red cell antibody screen performed with a 3-cell panel. In case of a positive screen, antibodies were further investigated using an 11-cell panel (BIO-RAD).
- 7 Urine detailed report (DR).

These data were retrieved from the laboratory information system and hard copies of transfusion reaction reports. Microsoft Excel 2013 was used for data entry and to calculate percentages.

RESULTS

During the study period, 20 956 blood components were issued, which included packed red cells (PRCs) 12 110 (58%), platelets 5979 (28%) and fresh frozen plasma (FFP) 2867(14%) units. Age of the patients ranged from 3 months to 65 years (mean age 16 years). A total of 32 (0.15%) ATRs were documented in 32 patients (16 male and 16 female patients), and the relative incidence of transfusion reactions by total blood components issued was found to be 0.19, 0.10 and 0.06% by PRCs, platelets and FFP, respectively. Types of transfusion reactions observed in this study and their comparison to other national and international studies are depicted in Table 1 (Khalid *et al.*, 2010; Bhattacharya *et al.*, 2011; Sousa Neto & Barbosa, 2011; Haslina *et al.*, 2012; Payandeh *et al.*, 2013; Gao *et al.*, 2015; Negi *et al.*, 2015; Sidhu *et al.*, 2015; Owusu-Ofori *et al.*, 2017).

The majority of reactions were minor allergic reactions (46.8%) (common presenting complaints were fever, chills, hives and rashes followed by dyspnoea, abdominal pain), followed by FNHTRs (28%). Bacterial contamination and AHTRs were rather frequent, i.e. 12.5 and 6.2%, respectively. Bacterial strains included *Staphylococcus epidermidis* in three platelet units and growth of pseudomonas species in one FFP bag, no bacterial contamination was found for RBC-related transfusion reactions. AHTR workup showed negative DAT, and an anti-E was identified in the patient's serum.

Table 1. Transfusion reactions in comparison to other studies

Transfusion reaction	Current study 2 years N = 32	Khalid <i>et al.</i> (2010) Pakistan 3 years N = 182	Sidhu <i>et al.</i> (2015) India 1 year N = 90	Negi <i>et al.</i> (2015) India 3 years N = 101	Bhattacharya <i>et al.</i> (2011) India 3 years N = 101	Gao <i>et al.</i> (2015) China Meta analysis N = 747	Payandeh <i>et al.</i> (2013) Iran 3 years N = 59	Haslina <i>et al.</i> (2012) Malaysia ⁹ 3 years N = 213	Sousa Neto & Barbosa (2011) Brazil 3 years N = 202	Owusu-Ofori <i>et al.</i> (2017) Ghana 1 year N = 88
Allergic reactions, N (%)	15 (46.8)	73 (40.1)	38 (42.2)	34 (33.6)	36 (35.6)	424 (56.7)	29 (49.1)	107 (50.2)	59 (29.2)	43 (48.8)
FNHTR, N (%)	9 (28)	89 (48.9)	33 (36.6)	26 (25.7)	43 (42.5)	297 (39.7)	22 (37.2)	81 (38.02)	114 (56.4)	26 (29.5)
Bacterial contamination, N (%)	4 (12.5)	2 (1.09)	2 (2.2)	-	4 (3.9)	-	-	-	5 (2.4)	-
Acute haemolytic reaction, N (%)	2 (6.2)	4 (2.1)	11 (12.2)	-	9 (8.9)	1 (0.1)	-	-	3 (1.4)	4 (4.5)
Anaphylactoid reaction, N (%)	1 (3.1)	-	1 (1.1)	-	4 (3.9)	-	-	-	-	-
TRALI, N (%)	1 (3.1)	-	1 (1.1)	6 (5.9)	1 (0.9)	-	-	-	-	-

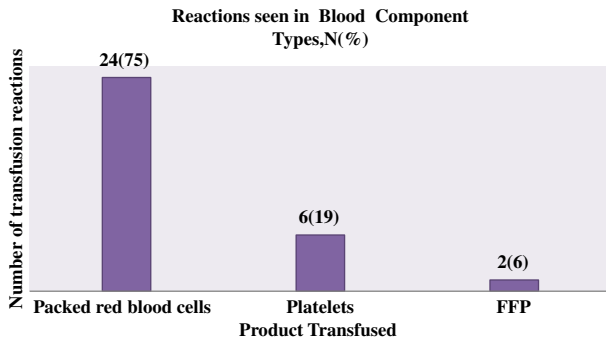


Fig. 1. Distribution of blood component types causing adverse reactions.

With regard to blood component types, the reactions were seen mostly with PRCs and are shown in Fig. 1.

DISCUSSION

The overall incidence of acute adverse reactions in our study was 0.15%, which is lower than the results various haemovigilance systems over the globe have reported. A study performed in India reported an incidence of 0.27% (Sidhu *et al.*, 2015). Another study performed in a health-care centre in India reported an incident rate of 0.2% (Negi *et al.*, 2015). A meta-analysis performed in China reported an incidence rate of 0.4%. However, a study conducted in Ghana reported an incidence of 21.3% (Owusu-Ofori *et al.*, 2017). The low incidence rate observed in our study could be due to underreporting of reactions, which probably has two reasons. One might be the lack of education regarding the diagnosis of transfusion reactions and importance of its reporting and the second may be because medical professionals fear negative personal consequences in case of medical negligence during blood transfusion. This clearly shows that Pakistan would benefit from a formal haemovigilance reporting system of adverse transfusion reactions.

The reactions reported in our study were primarily allergic, accounting for nearly half of the reactions. The addition of FNHTRs to this comprised three quarters of all ATR, despite the majority of patients being pre-medicated with chlorpheniramine and hydrocortisone along with acetaminophen that masks the onset of allergic reactions. Fortunately, the majority of our patients had minor symptoms like rash, hives and pruritus. This is somewhat comparable to the studies conducted in Pakistan (Khalid *et al.*, 2010), India (Sidhu *et al.*, 2015), Iran (Payandeh *et al.*, 2013) and Ghana (Owusu-Ofori *et al.*, 2017). However, other studies from India (Bhattacharya *et al.*, 2011; Negi *et al.*, 2015) and Brazil (Sousa Neto & Barbosa, 2011) reported a lower percentage of allergic reactions, whereas studies conducted in China (Gao *et al.*, 2015) and Malaysia (Haslina *et al.*, 2012) reported a higher percentage of allergic reactions. FNHTRs were the second most common adverse reaction seen in 28% of patients. Although this incidence somewhat reflects the studies conducted in Ghana (Owusu-Ofori *et al.*, 2017) and India,

(Negi *et al.*, 2015), it is considerably lower than that reported for other Asian health-care systems. However, other studies conducted nationally (Khalid *et al.*, 2010) and internationally (Bhattacharya *et al.*, 2011; Sousa Neto & Barbosa, 2011; Haslina *et al.*, 2012; Payandeh *et al.*, 2013; Gao *et al.*, 2015; Sidhu *et al.*, 2015), including India, reported a higher percentage of FNHTR as compared to the current study. This also indicates underreporting of transfusion reactions in our system. One of the reasons could be misinterpretation of FNHTR as febrile neutropenia. In-line leuko-depletion during blood component processing would likely reduce the incidence of the most frequent transfusion reactions in our patients. However, limited resources and financial constraints currently do not allow its implementation.

In our study, only one case of TRALI was reported after FFP transfusion. The most likely reason is that the majority of our blood donations are by male donors (99%) (Khurram *et al.*, 2017), but definitive diagnostic tests to confirm and establish TRALI are not available, which further challenges the apperception of this reaction. Furthermore, no case of volume overload was reported in our study, which is in contrast with the Serious Hazards of Transfusion (SHOT) report of the United Kingdom, where volume overload, i.e. transfusion associated circulatory overload (TACO), was one of the major morbidity- and mortality-related causes amongst transfusion-related adverse events (Bolton-Maggs, 2015). The most likely explanations are that our patients had a mean age of 16 years with a very low prevalence of cardiac impairment and our restrictive transfusion policy due to limited resources.

AHTRs in this study were 6.2%. This is somewhat comparable to the studies carried out in India (Bhattacharya *et al.*, 2011; Sidhu *et al.*, 2015) and Ghana (Owusu-Ofori *et al.*, 2017). However, other studies from Brazil (Sousa Neto & Barbosa, 2011), Pakistan (Khalid *et al.*, 2010) and China (Gao *et al.*, 2015) reported a lower percentage of AHTR, and it is necessary to further identify the reasons. During laboratory work-up of AHTR, we found alloantibodies. For this, we reviewed our Coombs cross-match method and plan on adding a red cells antibody screen on patients' pre-transfusion work-up to reduce the risk of AHTR due to alloimmunisation. All two AHTRs were caused by antigens, which are often matched in other medical systems for patients requiring a longer period of transfusion support. By testing blood donors as well as patients for Rhesus C, c, E, e and K in addition to ABO and Rhesus D, we would be able to avoid these transfusion reactions, as also emphasised by a previous study conducted in Pakistan (Zaidi *et al.*, 2015). This, however, would require substantial additional resources for typing reagents.

Interestingly, we did not encounter any ABO-mismatched blood transfusion reactions, which is quite contrary to the SHOT report of the United Kingdom, where a majority of incidents observed were a result of human clerical error (Bolton-Maggs, 2015, 2016). This indicates that our measures to reduce clerical errors, i.e. stringent cross checking at multiple levels from issuance of blood from the blood bank after group and cross-check verification by blood bank staff to cross check by day care staff and the treating physician, are

sufficient. Reactions caused by bacterial contamination after platelet transfusion was high in the current study as compared to the other studies (Khalid *et al.*, 2010; Bhattacharya *et al.*, 2011; Sousa Neto & Barbosa, 2011; Sidhu *et al.*, 2015). After we encountered bacterial contamination, we implemented stringent aseptic measures for the blood donors as this is the foremost aspect of haemovigilance (Bolton-Maggs, 2016), with careful inspection from the issuance of blood components to transfusion at the bed site. Similarly, blood bank temperature and products' storage conditions were carefully monitored. As we implemented these stringent measures in 2016, no further ATRs due to bacterial-contaminated platelet concentrates had been reported.

The relative incidence of transfusion reactions by total blood components issued was found to be 0.19, 0.10 and 0.06% by PRCs, platelets and FFP, respectively, with the greater number of transfusion reactions caused by pPRCs. This is similar to the study conducted by Haslina *et al.* (2012) and somewhat comparable with the findings of Khalid *et al.* (2010). One of the possible explanations for observing relatively higher reactions with PRCs could be the highest issuance of PRCs as compared to other blood components such as platelets and FFP. Secondly, our centre caters to thalassemia major as the bulk amongst the blood diseases requiring PRCs transfusion. These multi-transfused patients have a higher likelihood of developing transfusion reactions due to pre-immunisation.

To conclude, by comparing the frequency of transfusion reactions in the present study with the ones reported by others, we

realised that the incidence of ATRs was much lower. This indicates underreporting of ATRs in our system and strongly supports our efforts to now establish a haemovigilance system with proper recognition and documentation of transfusion reactions (Bolton-Maggs & Cohen, 2013). Although we may not be able to reduce the incidence of febrile and allergic transfusion reactions by universal leuko-depletion due to financial restrictions, we already successfully implemented changes in platelet concentrate production to reduce the risk of bacterial contamination. Furthermore, we are attempting to change pre-transfusion cross matching to reduce the risk of alloantibody-induced AHTRs through an improved Coombs cross-match method. This study shows that international benchmarking between different medical systems is helpful in improving transfusion safety.

DECLARATION OF CONFLICTING INTERESTS

The author(s) declare no potential conflicts of interests with respect to the authorship and/or publication of this article.

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M. B & N. A contributed as project leads of the study, contributed in the literature search and paper writing. H. T., N. F. and A. A. contributed to paper writing. I.N. contributed to the laboratory work. T. S. supervised the project and critically reviewed the manuscript. All authors reviewed the manuscript for important intellectual content and approved the final manuscript.

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