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ORIGINAL ARTICLE

# Non Infectious Complications Related to Blood Transfusion: An 11 year Retrospective Analysis in a Tertiary Care Hospital

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**Abstract** In India transmission of transfusion transmissible infections (TTI) has shown a relative decrease as a result of mandatory screening of donated blood for TTI's. However, reducing the incidence of non infectious complications poses a major challenge, mainly due to the fact that a number of adverse reactions go unreported. Blood transfusion reaction, can be categorized based on the time interval between transfusion of blood products and the presentation of adverse reactions as acute i.e. those presenting during or within 24 h and as delayed i.e. those presenting anytime after 24 h. Transfusion reactions can further be classified as immune and non immune or infectious and non infectious based on the pathophysiology. In this retrospective study which was undertaken with an aim to determine the type and frequency of non infectious complications due to transfusion of blood and blood products recorded the incidence of febrile non hemolytic transfusion reactions (FNHTR) 51.40 %, allergic reactions 40.14 %, non immune hemolytic reactions 4.22 %, hypothermia 2.81 %, anaphylaxis 0.70 % and iron overload 0.70 %. FNHTR which was found to be the most common complication in this study can certainly be minimized, if not completely eliminated by adopting a policy of universal leucodepletion, the implementation of which solely depends on the financial and infrastructure resources available. This study also reiterates the importance of hemovigilance as a tool to improve the safety of blood transfusion.

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**Keywords** Non infectious complications · Blood transfusion · Febrile non hemolytic transfusion reaction · Hemovigilance

## Introduction

Blood transfusion reaction defined as occurrence of any adverse event in the recipient during or after the transfusion of blood or blood components can be categorized based on the time interval between transfusion of blood products and the presentation of adverse reactions as acute i.e. those presenting during or within 24 h and as delayed i.e. those presenting anytime after 24 h [1]. Transfusion reactions can further be classified as immune and non immune or infectious and non infectious based on the pathophysiology.

In India transmission of transfusion transmissible infections has shown a relative decrease as a result of mandatory screening of donated blood by the use of highly sensitive and advanced laboratory tests [2]. However, reducing the incidence of non infectious complications poses a major challenge, mainly due to the fact that a number of adverse reactions go unreported. This might be due to lack of knowledge about their clinical presentation, overlapping of the adverse transfusion related presenting signs and symptoms and the clinical features of an already moribund patient, neglect of minor adverse reactions or the fear of being implicated.

Hemovigilance consists of collection and collation of data pertaining to adverse blood transfusion reactions, its analysis and policy making at a national level and its subsequent implementation to avoid such occurrences. The Hemovigilance Program of India which finds its roots from the European Hemovigilance network, being launched in 2012 is still in its infancy [3]. A lot needs to be done to

achieve the ultimate goal of being a part of the International Hemovigilance Network. The National Blood Policy of India introduced in 2002 mentions various steps to be taken to increase the awareness of Transfusion Medicine at the undergraduate and postgraduate level so as to sensitize the medical fraternity of the importance of early recognition as well as reporting of all such events [4].

This study was undertaken with an aim to determine the type and frequency of non infectious complications due to transfusion of blood and blood products in hospitalized patients as well as patients receiving them in the outpatient departments associated with our tertiary care hospital.

## Materials and Methods

Records of all the reported adverse transfusion reactions from January 2004 to November 2014 were preserved. An in depth retrospective analysis was done based on the clinical features and laboratory findings.

The reactions were reported to the blood bank on a transfusion reaction form which is issued along with the blood products intended to be transfused. All reactions were investigated as per the standard policy laid down by the Director General Health Services, Ministry of Health and Family Welfare, Government of India (Attached as image).

## Results

The total number of blood and blood components issued in the 11 year study period from January 2004 to November 2014 were 1,94,268 including 73,053 packed cell units and whole blood, 51,698 platelet units (both whole blood and apheresis derived) and 69,517 fresh frozen plasma (FFP) and cryoprecipitate. 76 of the 142 reactions (53.52 %) were attributed to packed red cell and whole blood units, 22 to platelet units (15.49 %) and 44 to FFP (30.98 %). None of the cryoprecipitate that was issued resulted in an adverse reaction. Out of 97,892 patients who received transfusions, 142 reportedly had adverse reaction (0.14 %). The frequency of transfusion reactions is as mentioned in Table 1. The risk associated with transfusion of each component is as shown in Table 2. 141 reactions reported were acute in nature and all were reported within 8 h of starting the transfusions. 1 delayed adverse reaction was found to be due to iron overload.

Various reactions observed are as under.

### Febrile Non Hemolytic Transfusion Reactions (FNHTR)

FNHTR was the most common adverse blood transfusion reaction in our study. 73 out of total 142 reactions were FNHTR i.e. 51.40 %. 58 patients developed FNHTR after transfusion of packed cell and whole blood units, 11

**Table 1** Frequency of transfusion reactions

| Transfusion reaction | Frequency | |
|---|---|---|
| | Number of patients | % |
| FNHTR | 73 | 51.40 |
| Allergic reactions | 57 | 40.14 |
| Non immune hemolytic reactions | 06 | 4.22 |
| Hypothermia | 04 | 2.81 |
| Anaphylaxis | 01 | 0.70 |
| TACO/TRALI | 01 | 0.70 |

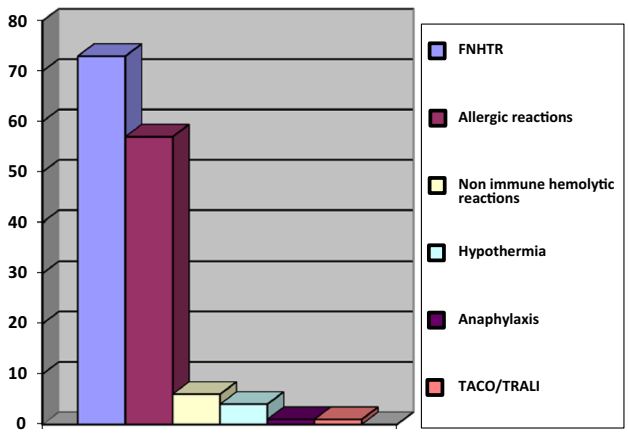

**Table 2** Transfusion reactions reported to various blood products

| Reaction | PRBC issued = 73,053 | | Platelets issued = 51,698 | | FFP/cryoprecipitate issued = 69,517 | |
|---|---|---|---|---|---|---|
| | Reaction reported | Reactions per 1000 | Reaction reported | Reactions per 1000 | Reaction reported | Reactions per 1000 |
| FNHTR | 58 | 0.79 | 11 | 0.21 | 04 | 0.05 |
| Allergic reactions | 07 | 0.10 | 10 | 0.19 | 40 | 0.54 |
| Non immune hemolytic reactions | 06 | 0.08 | – | – | – | – |
| Hypothermia | 04 | 0.05 | – | – | – | – |
| Anaphylaxis | – | – | 01 | 0.01 | – | – |
| TACO/TRALI | 01 | 0.01 | – | – | – | – |

patients after platelet units and 4 patients after FFP and cryoprecipitate.

### Allergic Reactions

They were noted in 57 out of 142 patients i.e. 40.14 %. 7 packed cell and whole blood units, 10 platelet and 40 FFP units were implicated in allergic reactions.

### Anaphylactic Reaction

There was 1 case of anaphylactic reaction to a transfused apheresis derived platelet unit which contributed 0.70 % of all the transfusion reactions. The estimated risk of anaphylactic reaction as per our study was noted as 0.01 per 1000 platelet units transfused.

### Hemolytic Transfusion Reactions

They are broadly categorized into acute or delayed and immune or non immune mediated. 6 out of 142 reactions were acute non immune hemolytic reactions i.e. 4.22 % of all reactions. There was no delayed and immune mediated hemolytic reaction.

### Hypothermia

There were 3 patients who were diagnosed to have hypothermia. This represented 2.11 % of all the transfusion reactions and all were reported in patients requiring massive transfusion.

### Iron Overload

This delayed reaction was reported 1 patient out of 142 after transfusion of 1 unit of packed cell, thereby contributing to 0.70 % of all reported reactions. The estimated risk of packed cell unit causing iron overload was found to be 0.01 per 1000 unit transfusions.

## Discussion

Only 142 patients out of 97,892 after transfusion of 1,94,268 blood and blood components reportedly had transfusion related adverse reactions i.e. an incidence of 0.07 %. Similar studies conducted by Praveen Kumar et al. and Bhattacharya et al. reported an incidence of 0.05 and 0.18 % of all blood products transfused [5, 6]. These figures represent only the tip of the iceberg and clearly indicate underreporting of transfusion related adverse reactions. Proper reporting of all adverse reactions, not only the minor ones but also the near misses will help understand the causality of such reactions and formulate safety related regulatory policies for better patient health care [7]. It helps identify priorities for transfusion safety and monitors effects of preventive measures without implicating any staff, physician or health care facility for the reaction. Success of this national hemovigilance program depends solely on truthful voluntary reporting of all adverse reactions Fig.1 describes the basic steps to be taken when confronted with a transfusion reaction.

FNHTR is defined as an increase in body temperature of 1 °C or more that occurs during or within several hours of transfusion and is unrelated to hemolysis, sepsis or other known causes of fever [8]. In FNHTR, the temperature rise is seen for no more than 8–12 h and is seemingly harmless except in patients with cardio respiratory compromise where in every 1 °C rise in temperature raises oxygen consumption by 13 % and shivering increases the oxygen demand by 300 % [9]. FNHTR's primarily caused by release of stored cytokines or due to leucocyte and platelet alloimmunization are generally not life threatening [10]. However they certainly do increase the cost of health care and increase the wastage of blood products. In our

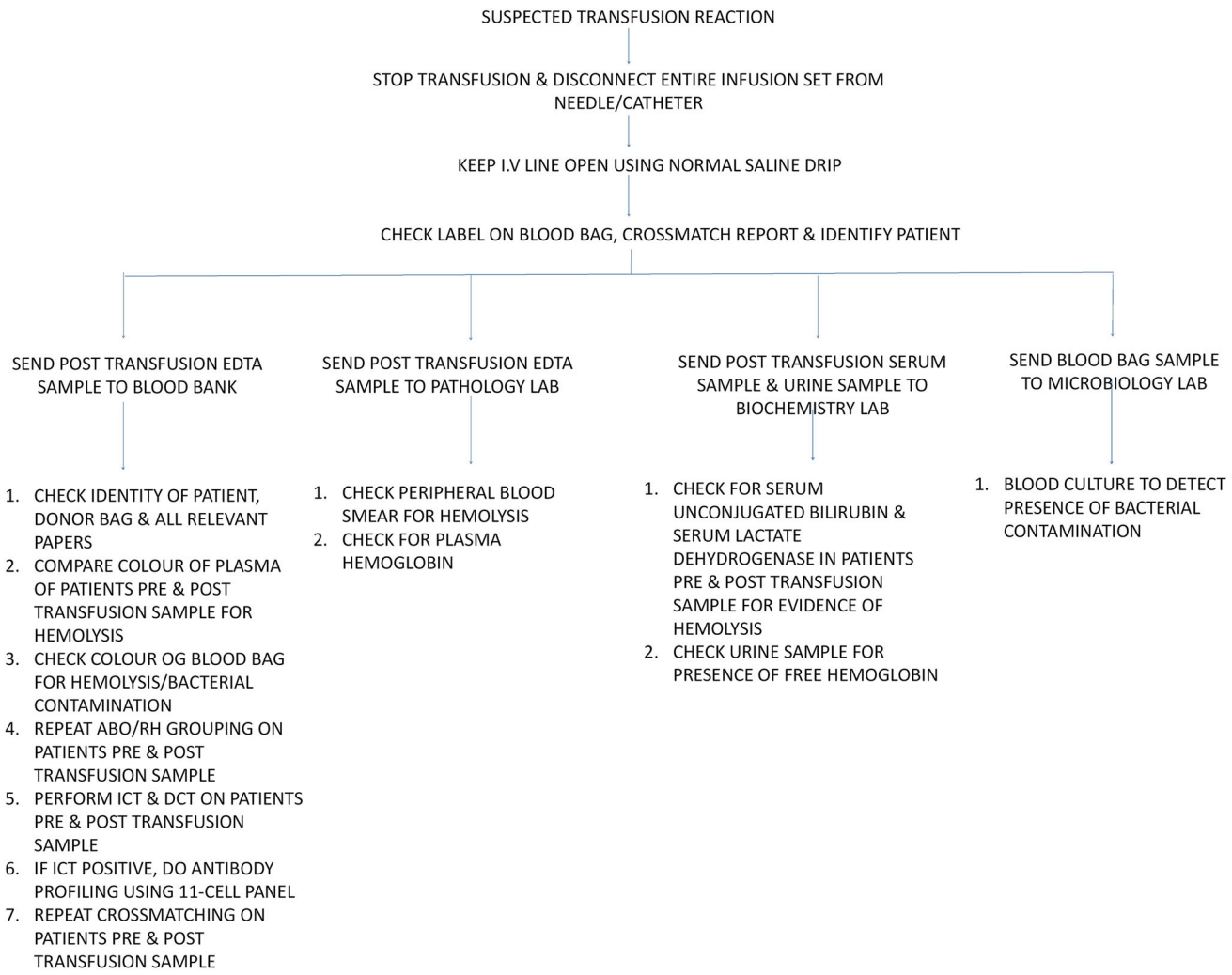


**Fig. 1** Algorithmic approach to the management of a transfusion reaction

study, 51.40 % of the reactions noted were FNHTR's. In comparison, a similar study by Praveen Kumar et al. 41 % of all reactions constituted FNHTR's [5]. After introducing mandatory universal leucoreduction for all multitransfused thalassemic children in 2003 at our center, there was a decrease in the incidence of FNHTR from 4 to 1 % as shown by a study conducted by Harsh Kumar et al. [11]. During the period of our study a total of 20,724 packed red cell units were transfused to the thalassemic patients, which means 1,73,184 blood and blood components were issued to patients other than thalassemics. If at all we were successful in reducing the incidence of FNHTR in the multitransfused thalassemic patients after the adoption of policy to provide leucodepleted blood products to these patients in 2003, it means that the incidence of FNHTR at our center is on the higher side as compared to other studies in patients other than thalassemics and steps need to be taken to address this. Leucoreduction serves the purpose of not only reducing the incidence of FNHTR, but also helps in reducing transmission of cytomegalovirus, risk of Transfusion associated graft versus host disease (TA-GvHD), potential alloimmunization to leucocyte and platelet antigens thereby decreasing the risk of Transfusion related adverse lung injury (TRALI) [12]. Leucoreduction can be done pre or post storage either by removal of the buffy coat using top and bottom method or by use of sophisticated leucofilters. Although the current high performance leucofilters reduce residual leucocyte content by 3–4 logs, an Indian study recommends the use of 1st log leucoreduction by the removal of buffy coat as a method to be universally applied for all cellular components in this resource short country [13].

Allergic and anaphylactic reactions constituted 40.14 and 0.70 % of all reactions in our study. The estimated risk of allergic reactions was calculated to be 0.10 per 1000 for packed cell and whole blood units, 0.19 per 1000 for platelet units and 0.54 per 1000 for FFP units. None of the cryoprecipitate that was issued resulted in any reaction.

This high incidence of allergic reactions in patients receiving plasma containing products can be attributed to the allergens present in them [14]. Anaphylactoid reactions are clinically similar to anaphylactic reactions but mechanisms other than IgE are responsible for their occurrence. Out of 142 patients, 1 presented with features suggestive of anaphylactic reaction after transfusion of apheresis derived platelets. The incidence of anaphylactic reaction is reported to be 1.7–4.3 per 100,000 red blood cell (RBC) and plasma transfusions and 62.6 per 100,000 platelet (PLT) pools [15]. The patient, diagnosed as a case of Myelodysplastic syndrome with Waldenstorm's macroglobulinemia presented with sudden breathlessness, fall in blood pressure and disoriented behavior immediately after transfusion of the blood component. The diagnosis of this rare but possible transfusion reaction was done based on the florid presenting symptoms. Serum IgE/IgA levels however could not be checked. Measures that can be taken to avoid further such reactions in IgA deficient patients are saline washing of red cell containing components, there by physically removing IgA and by transfusing blood components obtained from known IgA deficient donors [16, 17].

There were 6 cases of non immune hemolytic transfusion reactions which were diagnosed based on features suggestive of in vivo hemolysis as well as confirmed by further laboratory tests showing evidence of hemolysis and a negative DAT. Several reasons possible for this reaction to occur which include transfusion using smaller bore needles, applying external pressure on the blood product with pneumatic device at the time of transfusion leading to physical hemolysis, improper use of blood warmers causing thermal hemolysis, simultaneous transfusion of the blood product along with hypotonic solutions or pharmaceutical agents leading to osmotic hemolysis or even rarely by the transfusion of bacterially contaminated packed red cells [18]. Improper storage of the packed red cell units was found to be the cause of the reaction. In this connection, steps to be borne in mind during transfusion of blood and blood components in wards are mentioned as mentioned in Table 3.

**Table 3** An overview of clinical features of important non infectious adverse blood transfusion reactions

| Type | Clinical features |
|---|---|
| Acute | |
| Immune mediated | |
| Acute haemolytic transfusion reaction | Fever, chills/rigors, back pain, hypotension, haemoglobinuria, pain along IV line, bleeding diathesis |
| Febrile nonhaemolytic transfusion reaction | Rise in temperature >1 °C, chills and/or rigors, discomfort, vomiting, flushing |
| Urticarial | Pruritus, urticaria, or flushing |
| Anaphylactic | Hypotension, urticaria, bronchospasm, stridor, local oedema |
| Transfusion related acute lung injury | Hypoxemia, noncardiogenic pulmonary oedema, respiratory failure, hypotension, fever, cyanosis |
| Non immune mediated | |
| Transfusion related sepsis | Fever ≥102 °F, chills, hypotension within 90 min of transfusion |
| Non immune haemolysis | Features of intravascular haemolysis of red cells, namely, haemoglobinuria, haemoglobinemia |
| Transfusion associated circulatory overload | Signs of congestive heart failure, shortness of breath, wheezing, hypertension |
| Delayed | |
| Immune mediated | |
| Delayed haemolytic transfusion reaction | Fever, decreasing haematocrit, mild icterus with other features of haemolysis |
| Alloimmunization to red cell antigens, platelets and leukocytes (HLA) | Haemolytic disease of fetus and newborn, delayed serologic reaction, platelet refractoriness |
| Transfusion associated immunomodulation | Increased chances of postoperative infections, cancer recurrence, multiple organ dysfunction |
| Transfusion associated graft versus host disease | Rash, watery diarrhoea, fever, anorexia, vomiting, abnormal liver function tests, bone marrow failure |
| Posttransfusion purpura | Thrombocytopenia, purpura, bleeding |
| Non immune mediated | |
| Iron overload | Diabetes, cardiomyopathy, cirrhosis |

Four patients developed hypothermia following massive transfusion. In all four cases it was found that the packed cell units which were transfused were not suitably warmed, there by indicating the estimated risk of hypothermia following packed cell transfusion to be 0.04 per 1000 units transfused. All patients were managed symptomatically and were revived in time.

One multitransfused thalassemic 11 year old patient presented with symptoms of chills and rigors and chest pain after transfusion of 150 ml of packed cells. There was a steep fall of blood pressure and she also developed respiratory failure with bilateral crepts. She was intubated and ventilated but later on developed septicemia and died of multiple organ failure and disseminated intravascular coagulation. The patient was found to have suffered from Transfusion Associated Iron Overload (TACO)/Transfusion Associated Acute Lung Injury (TRALI) based on the presenting clinical features; however the post mortem findings indicated hemochromatosis of lung possibly due to iron overload.

One patient having a posterior fossa space occupying lesion who underwent craniotomy developed a fall in blood pressure along with concurrent administration of packed red cell unit. This incident was thoroughly investigated and the sharp fall in blood pressure was attributed to an intra operative blood loss. We do appreciate reporting of such cases as it not only helps the blood bank scrutinize its working policies and procedures but also leads to the best possible patient health care by imbibing a coordinating effort of all departments in doing so.

There was no adverse reaction due to contamination of blood units which indicates that all sterile precautions were taken during collection, handling and processing of blood and blood components. Also there was no case of acute or delayed immune mediated hemolytic reaction. This has been largely possible due to the use of highly sensitive gel card technology and proper procedures and policies are in place for identification of the recipient, cross matching, antibody screening and issue of blood and blood components. Also, no or very few cases of TACO, TRALI or delayed transfusion reaction were noted. This may be due to underreporting, lack of knowledge of the same by clinicians or the nursing staff or the fact that the patients transfused were severely ill patients admitted in the intensive care unit.

The global success of hemovigilance was jointly discussed at a world forum in 2012 organized by World Health Organisation in collaboration with the International Haemovigilance Network and the International Society of Blood Transfusion. This leaves us in no doubt about the ever increasing role of reporting each and every case of adverse blood transfusion reaction including the minor ones and also the near misses. The importance of Hospital transfusion committee and hemovigilance needs to be emphasized.

## Conclusion

This study found the incidence of adverse non infectious blood transfusion reactions to be 0.07 % (142 out of 1,94,268). Majority of the reactions were found to be due to FNHTR. This certainly can be minimized, if not completely eliminated by ULR. However, the decision of implementing ULR solely depends on every institutions financial and infrastructure capability and availability. Although comparable with studies conducted elsewhere, it reiterates the importance of hemovigilance as a tool to improve the safety of blood transfusion [19].

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