Research Article

Transfusion-related acute lung injury (TRALI) – Blood transfusion complication

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Received April 1, 2015. Accepted April 17, 2015

Abstract

Background: The blood transfusion reactions occur during or after transfusion. The untoward affect vary from being relatively mild to lethal. Some of them can be prevented while others cannot. Transfusion-related acute lung injury (TRALI) is an uncommon, probably unrecognized complication of transfusion of plasma containing blood components, which is characterized by acute respiratory distress. It is diagnosed when acute lung injury (ALI) occurs during or within 6 h of transfusion in a patient without preexisting ALI in the absence of alternative risk factors such as sepsis, shock, and cardiac failure for ALI.

Objective: To study the blood transfusion reactions in the recipient, a study was carried out over a period of 3 years in Government Medical College and Acharya Shri Chander College of Medical Sciences (ASCOMS), Jammu – two tertiary-care centers of the region.

Materials and Methods: In a retrospective study, over a period of 3 years (January 2008–January 2011), transfusion reactions were analyzed in two tertiary-care centers in the Department of Transfusion Medicine of Government Medical College and Acharya Shri Chander College of Medical Sciences (ASCOMS), Jammu.

Results: The total number of transfusions given in these two tertiary-care centers during 3-year study period was 68,290 with 3% of overall incidence of transfusion reactions, which is insignificant with the incidence of febrile reactions being highest (1.63%) and that of TRALI being lowest (0.0029%).

Conclusion: Blood banks did not have facility for demonstrating human leukocyte antigen class antibody or leuko-agglutinins in the blood donors. However, majority of blood donors were males repeat voluntary donors and previously not implicated in any blood transfusion reaction. The pre-transfusion cross-matching procedures were compatible. The possibility of trauma or injury may be the pathogenic trigger for TRALI.

KEY WORDS: Transfusion reactions, acute respiratory distress, TRALI.

Introduction

Blood transfusions are indicated in alteration of blood in either quality or quantity that interferes with the normal functions of the body. Most commonly it is indicated pre- or post-operatively in building-up and making up the loss; in blood loss such as accidents and surgical operations; blood disorders such as hemophilia, purpura, clotting defect; and blood diseases such as severe anemia, leukemia, and blood dyscrasia.

Access this article online	
Website: http://www.ijmsph.com	Quick Response Code:
DOI: 10.5455/ijmsph.2015.01042015275	

Besides incompatible blood transfusion leading to the hemolytic transfusion reaction, other transfusion reactions occurring in the recipients of blood transfusion are febrile reactions, allergic and anaphylactic reactions, circulatory overload, rarely immunologic complications, and transfusion-related acute lung injury (TRALI).

Zah et al. in a review article reported that the first case of fatal pulmonary edema following transfusion was reported in 1950.[1] Non-cardiogenic lung edema, as a result of blood

Table 1: Criteria for diagnosis of TRALI: Conference Committee 2004 and European Haemovigilance Network

(a)	Acute onset of acute lung injury (ALI)
(b)	Hyoxemia PaO_2/FiO_2 (i.e. ratio of partial pressure of arterial O_2 to the fraction of inspired O_2) Or O_2 saturation <300 (SpO_2 < 90%) Or other clinical evidence
(c)	Bilateral lung infiltrates on frontal chest radiograph
(d)	No evidence of left arterial hypertension (i.e. transfusion-associated circulatory overload)
(e)	Occurrence during or within 6 h after completion of transfusion
(f)	No temporal relation to an alternative risk factor
(g)	New ALI and no other ALI risk factors present (aspiration, multiple trauma, pneumonia, cardiopulmonary bypass, burn injury, toxic inhalation, lung contusion, pancreatitis, drug overdose, drowning, shock, and severe sepsis)

Table 2: Number of patients showing transfusion reactions over a period of 3 years

Blood transfusion reactions	Total transfusions given in 3-year study period = 68290	
	No. of patients	Percentage (%)
1. Febrile reactions	1116	1.63
2. Allergic reactions	320	0.47
3. Circulatory overload	600	0.88
4. Hemolytic transfusion reaction	10	0.015
5. TRALI	2	0.0029
6. Immunologic complications	nil	Nil
Overall incidence	2048	3.00

transfusion was first described by Barnard in 1951.[2] After Barnard's initial description, it was reported using various names including non-cardiogenic pulmonary edema, pulmonary hypersensitivity, and severe allergic pulmonary edema. Popovsky et al. recognized this transfusion reaction as a distinct clinical entity and coined the term transfusion-related acute lung injury.[3]

Popovsky and Moore analyzed 36 TRALI patients receiving blood transfusion and concluded that surgical procedures and infections induce neutrophil priming in patients.[4] Silliman et al. conducted prospective study of TRALI reactions in 81 patients with hematological malignancies and cardiac disease and identified them at risk for TRALI. All TRALI reactions were secondary to transfusion of stored platelets and red cells.[5]

In 2004, the European Haemovigilance Network (EHN) proposed criteria for the diagnosis of TRALI, which is summarized in Table 1.[6]

Holness et al.[7] and Stainsby et al.[8] in 2004 postulated that TRALI is the most common transfusion-related fatality in the USA and the UK. Gajic and Moore[9] evaluated the incidence of TRALI among a cohort of transfused medical intensive care unit and reported 74 TRALI cases from 901 observed patients and 6558 associated blood products. The greater proportion of patients had gastrointestinal and liver disease and others had ALI risk factors highlighting close interaction between risk factors and subsequent development of ALI. Bux[10] analyzed transfusion reaction in the UK and the USA and showed that TRALI is among the most common causes of fatal transfusion reactions.

With handful of literature available on TRALI in trauma patients, this study was undertaken to observe the blood transfusion reaction in the tertiary-care centers of Jammu over a period of 3 years from January 2010 to January 2013.

Total number of transfusion given in the two tertiary-care centers during 3-year study period was 68,290. The overall incidence of blood transfusion reactions was 3%. An unusual type of blood transfusion reaction TRALI was observed in two cases of trauma. Both of them had received leuko-reduced buffy coat depleted red cells from healthy male donors for correction of anemia pre-operatively and were awaiting surgery. The literature was reviewed to ascertain the cause of this rare, life-threatening complication in trauma patients.

Materials and Methods

In a retrospective study, over a period of 3 years (January 2008–January 2011), transfusion reactions were analyzed in the two tertiary-care centers in the Departments of Transfusion Medicine of Government Medical College and Acharya Shri Chander College of Medical Sciences (ASCOMS), Jammu. The Departments of Transfusion Medicines issued a total of 68,290 blood bags for transfusion in 3 years (January 2008–January 2011) to the Clinical Departments of Surgery, Medicine, Obstetrics and Gynaecology, Orthopaedics and Emergency Services.

The various transfusion reactions observed were febrile reactions, hemolytic transfusion reactions, circulatory overload, allergic and anaphylactic reactions. During the study period, two cases of TRALI (non-cardiogenic pulmonary oedema) were also observed in the tertiary-care centers. The first case occurred in a male who received leukoreduced red blood cells after road traffic accident and other case occurred in multiparous female with Colle's fracture after trauma.

TRALI is defined as an ALI that is temporarily related to blood transfusion, especially if it occurs within first 6 h of transfusion. It is an uncommon syndrome characterized by acute respiratory distress following transfusion. TRALI reactions have equal gender distributions and can occur in all age

groups. All blood products except albumin have been implicated in TRALI reactions.[11] TRALI has been reported from all types of blood components including whole blood, red cells, aphaeresis platelets, whole blood platelets, fresh frozen plasma, cryoprecipitate, granulocytes, stem cell products, and even intravenous immunoglobulin preparations.[4] True incidence of TRALI is unknown but different estimates have been made. According to the literature, the incidence is 1:5000 for blood components.[3]

Pathogenesis of TRALI

(1) *Priming response of neutrophils is activated*: Priming is the process whereby the response of neutrophils to an activating stimulus is potentiated. It facilitates the clustering of surface receptors, such as FcrRIIa and β-integrins, and the formation of the NADPH complex that causes synthesis of reactive oxygen species. Priming is triggered by the transfused blood component and necrotic cells that release platelet activating factor (PAF), tumor necrosis factor (TNF-α), interleukin-8, granulocyte/macrophage-colony stimulating factor, and interferon-γ.
(2) *Activation of pulmonary endothelial cells*: Activated pulmonary endothelial cell upregulate receptors such as L-selectin, P-selectin, and ICAM-I that allow neutrophil adhesion.[12]
(3) *Priming substances in blood component*:
    a. Leukocyte antibodies
    b. Antibodies to human neutrophil antigens
    c. Bioactive lipids: Blood components accumulate intermediate metabolic products, such as bioactive lipids and lysophosphatidylcholine species (C_{16}, C_{18}, lyso-PAF), which are breakdown products of membrane lipids.
    d. Other factors: CD40L is present in platelet concentrates. CD40L binds to the CD40 that is present on the surface of monocytes, macrophages, and also neutrophils.[13]

Results

The total of 68,290 transfusions given in the two tertiary-care centers during the 3-year study period with the overall incidence of transfusion reactions of 3%, which is insignificant with the incidence of febrile reactions being highest (1.63%) and that of TRALI being least (0.0029%). No significant variation was recorded in the overall distribution pattern of blood transfusion reaction each year during the study period.

Discussion

TRALI is among three leading causes of transfusion-related fatalities along with ABO incompatibility and bacterial contamination. It is associated with high morbidity with majority of patients requiring ventilatory support. However, the lung injury is transient with PO_2 levels returning to pre-transfusion levels within 48–96 h and chest X-ray returning to normal within 96 h. In this study, 68,290 transfusions were given during 3-year study period (conducted in two tertiary-care centers) and with 3% overall incidence of transfusion reactions including TRALI which contributed only .0029%. Pre-transfusion and post-transfusion cross-matching procedures were compatible. The trauma and possibility of release of biological mediators in two patients or priming activating substances present in blood components may be the pathogenic trigger for TRALI.

Our study is analogous to the study conducted by Popovsky and Moore, who analyzed 36 TRALI patients receiving blood transfusion.[4] Thirty-one of 36 TRALI cases occurred in patients with surgical procedures (n = 24) or by postoperative blood loss (n = 7) and remaining 5 cases occurred in patients with anemia for chronic conditions. Popovsky and Moore concluded that surgical procedures and infections induce neutrophil priming in patients.

Our study of analysis of transfusion reactions over a period of 3 years is analogous to prospective study conducted by Silliman et al.[5] on patients with hematological malignancies and cardiac disease who were at risk of TRALI.

Prevention

Primary prevention refers to measures taken to reduce TRALI that is to institute the use of predominantly male plasma for preparation of high volume plasma components, such as frozen plasma, fresh frozen plasma, cryosupernatent plasma, plasma for resuspension of platelet pools, and decrease the use of plasma from donors at high risk for human leukocyte antigen (HLA) immunization, for example, previously pregnant ladies, multiparous ladies.

Secondary prevention refers to the management of donors temporarily associated with TRALI or with possible TRALI reaction. These include: (1) implicated donor with antibodies to HLA Class I or Class II antigens or human neutrophil antigen. In case of positive cross-match reaction, the donor is deferred; (2) associated donor is associated with a TRALI reaction if blood was transfused during the 6 h preceding the first clinical manifestation of TRALI. If negative cross-matched reaction is noticed then it is used for washed RBC and plasma for fractionation.

This study was conducted to analyze the transfusion reactions of blood bags issued by the Department of Transfusion Medicine and complete follow-up of the patient during and after transfusion.

In this study though the incidence of TRALI was very insignificant still it is unlikely that TRALI can be entirely prevented but its frequency may be reduced by judicious use of blood components; blood conservation programs that minimize unnecessary transfusion; interventions by blood collecting facilities to minimize the preparation of high plasma volume components from donors with antibodies to leucocytes, such as pregnant ladies and multiparous ladies; and deferring the donors who have been associated with TRALI reactions.

However, this study has many limitations because it is restricted to the overall transfusion reactions in only two available tertiary-care centers, both of which are in Jammu division only but not in Kashmir division. Moreover, the blood banks did not have facility for demonstrating HLA class antibody or leukoagglutinins in the blood donors.

Blood banks should be well equipped with adequate facilities for screening of donor blood for HLA antibodies and trained hospital medical staff to have high index of suspicion in order to diagnose TRALI appropriately. All cases of TRALI should be reported to blood bank.

Conclusion

In this study, the Blood Banks did not have facility for demonstrating HLA class antibody or leukoagglutinins in the blood donors. However, majority of blood donors were male repeat voluntary donors and previously not implicated in any blood transfusion reaction. The pre-transfusion cross-matching procedures were compatible. The possibility of trauma or injury may be the pathogenic trigger for TRALI. Further studies of occurrence of TRALI in relation to trauma and sepsis are needed along with implementation of preventive measures, including Donor Referrals for blood safety and to avoid adverse blood transfusion reaction.

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How to cite this article: Sharma N, Sharma K. Transfusion-related acute lung injury (TRALI) – Blood transfusion complication. Int J Med Sci Public Health 2015;4:1343-1346

Source of Support: Nil, **Conflict of Interest:** None declared.