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Transfusion -Related Acute Lung Injury (TRALI): Incidence, Risk Factors and Outcome in The Cardiothoracic Intensive Care Unit

KEYWORDS: cardiopulmonary bypass, platelets, transfusion- related acute lung injury, TRALI

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ABSTRACT *BACKGROUND: Transfusion –related acute lung injury (TRALI) is a life threatening complication of blood transfusion. Cardiac surgery under cardiopulmonary bypass is a risk factor for acute lung injury(ALI) . The term" possible TRALI " is used when there are alternative risk factors for ALI in addition to blood transfusion.*

OBJECTIVES OF THE STUDY: To determine the incidence, outcome and risk factors of " possible TRALI " in the cardiothoracic intensive care unit.

MATERIALS AND METHODS: It was an observational prospective cohort study in patients who underwent cardiac surgery and received perioperative blood transfusion. Perioperative patient related, surgery related and transfusion related data were recorded.

RESULTS: The incidence of "possible TRALI" was 5.4%. The APACHE 2 score (p= 0.032) and platelet transfusion (p=0.035) was significantly higher for the "possible TRALI" group compared to the no lung injury group. There was no mortality. The duration of ventilation and ICU stay was comparable between both the groups.

CONCLUSION: The incidence of possible TRALI is high (5.4%) in cardiac surgery. The occurrence of TRALI is highest for platelet transfusion.

INTRODUCTION :

Transfusion –related acute lung injury (TRALI) is a life threatening complication of blood transfusion. It is one of the leading causes of transfusion related deaths. [1] TRALI is a clinical syndrome characterized by the onset of respiratory distress temporally related to transfusion of blood or blood components[2]. TRALI is underdiagnosed and under reported due to a lack of an international definition for it and a lack of awareness [2] . A consensus panel and the US National Heart, Lung and Blood Institute Working Group in 2004 formulated a definition for TRALI based on clinical and radiological parameters .[1, 3, 4] The term 'suspected TRALI' is used if there is acute lung injury (ALI) within 6 hours of transfusion in the absence of another risk factor. If both transfusion and another risk factor for acute lung injury are present, the term "possible TRALI " is used. The term 'delayed TRALI ' is applied if lung injury occurs 6-72 hours after transfusion. [5]

There are various hypotheses on the etiology of TRALI. The first is antibody mediated TRALI which is due to the passive transfusion of human leukocyte antigen (HLA) or human neutrophil antigen (HNA) and corresponding antibodies from the donor directed against antigens of the recipient. Another theory is the two hit hypothesis. The first hit is primary inflammatory condition which causes adherence of primed neutrophils to the pulmonary endothelium. The second hit is the transfusion of any blood product containing antibodies or factors that accumulate during storage which activate the pulmonary neutrophils and endothelial cells bringing about capillary leakage and consequently pulmonary oedema . [6]

Common causes of acute lung injury include aspiration pneumonia, sepsis, trauma, etc [2].

Cardiopulmonary bypass (CPB) is also a risk factor for ALI. [6] Lung dysfunction is attributed to anti-inflammatory response initiated by the contact of blood cells with the foreign surface of the bypass circuit. During CPB the lungs are deflated and non-ventilated, which may cause injury to the lung vasculature (the "first event"). In addition, the use of CPB can cause neutrophil priming. [7,8]

Because cardiopulmonary bypass is itself a risk factor for ALI, our patients were analyzed for "possible TRALI ". [9]

The aim of this study was to determine the incidence and outcome of "possible TRALI" in patients admitted to the cardiothoracic intensive care unit(ICU) who were transfused at least one unit of blood or blood product. We also wanted to evaluate the risk factors for " possible TRALI ".

MATERIAL AND METHODS :

This was an observational prospective cohort study conducted in a large tertiary care hospital. The study was approved by the institutional review board and ethics committee (No.6039). The duration of the study was 16 months and included 149 patients who underwent coronary artery bypass grafting (CABG) under CPB.

Study population:

Patients above 18 years of age who underwent CABG under CPB and were transfused at least one unit of blood or blood component intra-operatively or within 24 hours post-operatively in the ICU were included. Patients who had any risk factor for ALI except CPB were excluded.

All patients had a baseline preoperative chest radiograph and an intraoperative arterial blood gas (ABG). Technique of anaesthesia was according to our department protocol.

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Cardiopulmonary bypass was performed under mild hypothermia (32-34°C), using a membrane oxygenator and a nonpulsatile blood flow. Haemoglobin on pump was maintained between 6-8 gm %. Standardized perioperative monitoring included invasive arterial and central venous pressure monitoring throughout surgery and post operatively in the ICU for all patients.

The diagnosis of possible TRALI was made on the following criteria [6]

1. Acute lung injury- PaO2/FIO2 < 300 mmHg, bilateral pulmonary infiltrates on chest radiograph, PEEP(positive end expiratory pressure) or CPAP(continuous positive airway pressure) ≥5 cmH2O, no signs of hydrostatic pulmonary edema (central venous pressure ≤ 15 mmHg or pulmonary arterial occlusion pressure ≤ 18 mmHg)

2. No pre-existing ALI before transfusion

3. Onset of signs during or within 6 hours of transfusion

4. A clear temporal relationship to an alternative risk factor for ALI (cardiopulmonary bypass)

After surgery all patients were shifted to the cardiothoracic ICU and electively ventilated. Routine blood investigations, blood gases, chest radiographs were taken on admission to ICU and on each day during their stay in the ICU. ABG`s and chest x-rays done within six hours of transfusion were used for diagnosis. Blood gases were done every 6 hours for the first 24 hours. The postoperative ICU protocol involved blood transfusion to maintain hemoglobin concentration above 8 gm% using whole blood (WB) or red blood cells (RBCs), fresh frozen plasma (FFP) when Prothrombin time/ International Normalised Ratio (PT/INR) was more than 1.5, platelets concentrate when platelet count was less than 50,000 and cryoprecipitate when fibrinogen was less than 100 mg/dl. Adrenaline and noradrenaline infusion were utilized to achieve mean arterial blood pressure of ≥65 mm Hg, and milrinone was added if there was left or right ventricular dysfunction or pulmonary artery hypertension.

The measurement of severity of illness was done by the APACHE 2 (Acute Physiological and Chronic Health Evaluation 2) and Severity of Disease Classification System Scoring. It was done for every patient within one hour of admission to the ICU. The PaO2 /FiO2 ratio, PEEP, and chest radiograph scoring were calculated each day until day of discharge from the ICU. Patients who did develop "possible TRALI" were followed up until they recovered or until death. Mortality was defined as in hospital death.

The outcome data was collected as duration of ventilation, length of ICU stay and in hospital mortality.

Infiltrates on chest radiographs were defined as opacities that cannot be explained completely by pleural effusions, mass, body habitus or collapse. Daily chest radiographs were analysed and interpreted by two critical care physicians who were blinded to the clinical status of the patient.

Data collection:
All patient related, surgery related and transfusion related data was collected and entered in the standardized proforma to evaluate for risk factors for "possible TRALI ".

Statistical Analysis
Continuous data were presented as mean ± SD. Mean values were compared by the student`s t test. Pearson`s Chi square test was used for comparing the proportions. Univariate analyses were performed using Fisher's exact test for dichotomous variables. The non parametric Mann-Whiteley U test was used to analyze the highly skewed variables of duration of ventilation and duration of ICU stay. A p value of <0.05 was considered statistically significant. All analyses were conducted using SPSS 16.0(Statistical Package for Social Sciences)

RESULTS :
Incidence of possible TRALI
During the 16 month study period, 149 post-CABG patients were included. Of these 8 patients (5.4%) fit the criteria for "possible TRALI". There was no lung injury in 137 (91.9%) patients. Four (2.7%) patients had ALI that occurred more than 6 hours after transfusion. These patients were grouped as 'delayed TRALI' (Table 1). These patients were not included in the rest of the analysis. Of the 8 patients who had "possible TRALI", 2 met the criteria for Acute Respiratory Distress Syndrome (ARDS).

Table 1. Incidence of possible TRALI

	Incidence (no. with possible TRALI / no. at risk)	Percentage (%)
Possible TRALI	8/149	5.4
No Lung Injury	137/149	91.9
Delayed TRALI	4/149	2.7

Demographic and clinical characteristics and analysis of risk factors for possible TRALI

In the study, the bulk of the patients fell between the age group of 35-75 years. The mean age for the "possible TRALI" group was 60.25 years and for the no lung injury group was 57.17 years. There was no statistical significance (p=0.068) (Table 2)

The Fisher`s exact test suggested that there was no significant association between the gender and the outcome, although there appeared to be a higher incidence of "possible TRALI" - 2 out of 17 (11.76%) in the female sex compared to 6 out of 128 (4.68 %) in the male sex. This was statistically insignificant (p =0.237)(Table 2)

On univariate analysis of the clinical variables, the APACHE 2 score at admission for those patients who developed "possible TRALI"was higher compared to the no lung injury group and it was statistically significant with a p value of 0.032 . There was no significant association betweeen diabetes (p=0.147), hypertension(p=>0.99), and smoking(p=>0.99) with the development of "possible TRALI". The duration of cardiopulmonary bypass was less in the " possible TRALI "group but not statistically significant (p=0.613) (Table 2)

Table 2 .Demographic and clinical characteristics of patients with "possible TRALI" and no lung injury.

	No Lung Injury (n=137)	Possible TRALI (n=8)	p value
Age in years, mean ±SD	57.17±8.2	60.25±3.8	0.068

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Gender – Female, n (%)	15(10.94)	2(25.0)	
Male	122(89.05)	6(75.0)	0.237
Diabetes, n (%)	62	6	0.147
Hypertension, n (%)	78	5	>0.99
Smoking, n (%)	63	4	>0.99
APACHE 2 (mean± SD)	8.64±2.812	10.88±3.182	0.032
CPB time(minutes ,mean± SD))	82.15±17.97	78.88±12.01	0.613
Ventilation(days)	2	2	NA
ICU stay(days)	2	2	NA

Transfusion related risk factors

On analysis of the components transfused, there was a significant association between platelet transfusion and the development of "possible TRALI" (p=0.035). We did not find an association between the transfusion of WB, RBCs, FFP and cryoprecipitate with the development of "possible TRALI.(Table 3)

Table 3. Transfusion data in patients with" possible TRALI" and no lung Injury

Type of blood product	No lung injury N=137	Possible TRALI N=8	P value
Whole blood	101	6	>0.99
Red Blood Cells	57	3	>0.99
Fresh Frozen Plasma	47	3	>0.99
Platelets	22	4	0.035
Cryoprecipitate	1	0	>0.99

Outcome

The total duration of ventilation and ICU stay was comparable in both the groups with the mean being 2 days (p >0.99). There was no in hospital mortality in both the groups (Table 2)

DISCUSSION :

Incidence of possible TRALI

As per criteria, 149 CABG patients were analyzed. Eight were diagnosed with "possible TRALI" giving an incidence of 5.4%. In a study done by Rana R et al [10] the incidence was 1% (14 out of 1352 cases) for "possible TRALI ". Zah-Bogović et al got an incidence of 12.2% for post CPB patients. They monitored for up to 24 hours (including cases of delayed TRALI).[11] If they observed the typical 6 hours, it would be 8%. Vlaar et al got an incidence of 2.4% for post CPB patients. [7,8] Gajic O et al [12] found that in mechanically ventilated patients who received transfusion the incidence was 33%. The higher incidence was probably because they monitored for 48 hours.

A few patients had PaO2/Fio2 ratio <200, which was ARDS. The incidence of ARDS in this study amongst "the possible TRALI" patients was 1.3% (2 out of 149). In a study done by **Milot J** et al [13], the incidence of ARDS was 0.4% in post CPB patients and compared to the control group, these patients received more blood products. Koch CG et al [14] demonstrated that transfusion considerably increases the risk for every morbid outcome (including pulmonary dysfunction) in patients who undergo CPB. Our incidence cannot be attributed to CPB alone. As the patients did not have any other risk factor for ALI, we attributed this to transfusion. Our patients, by undergoing CPB were likely to have had an underlying "first event" and were at a higher risk for developing TRALI when transfused. [3]

Incidence in relation to blood products

Our study had a statistically significant correlation between platelet transfusion and "possible TRALI". An incidence of 1 in 59 units transfused. The study done by Zah-Bogović et al [11] showed that patients with "possible TRALI " received more platelets, plasma and blood units. Vlaar et al [7] also found similar finding. The incidence of possible TRALI per product transfused was 0.61% for them. Rana R et al [10] got an incidence of 1 in 534 units for "possible TRALI" and 1 in 1271 units transfused for 'suspected TRALI'. There have been various studies implicating different components being associated with the development of 'suspected TRALI'. Silliman et al [15] found that platelets were implicated in 74 of 90 TRALI cases. Gajic O et al [12] identified FFP transfusion as a main risk factor for the development of TRALI. Wallis et al [16] implicated FFP transfusion for 10 out of 11 of their TRALI cases. Clarke et al [17] implicated platelet transfusion as a risk for developing TRALI. Khan et al [18] found that FFP and platelet transfusion were associated with the development of ALI in critically ill patients. Popovsky et al [19] reported an incidence of 1 in 5000 blood products transfused. Sillman et al [15] reported an incidence of 1 in 1323 blood components used. When multiple units are transfused, there is a greater risk of infusion of a unit containing antileukocyte antibodies, biologically acting substances or both which can cause TRALI.

Demographic and clinical characteristics

The patients with "possible TRALI" had higher APACHE 2 scores which in turn indicated greater severity of illness as compared to those without lung injury. In Vlaar et al`s [7] study, the "possible TRALI" patients had higher American Society of Anaesthesiologists (ASA) score and Euroscore and in Zah-Bogović et al`s [11] study they had higher ASA score indicative of higher surgical risk. Gajic O et al [12] who used the APACHE 3 scoring system in his study did not find any such association.

Our study did not find any increased risk for "possible TRALI" in association with age, sex, history of smoking and presence of diabetes or hypertension. Gajic O et al [12] and Zah-Bogović et al [11] had similar findings but Vlaar et al [7] founder the "possible TRALI" patients were older. Our study found that the duration of CPB did not appear to cause an increased risk for lung injury. **Milot J** et al [13] found that rather than the CPB time, it was the increased number of blood transfusions that caused lung injury. Zah-Bogović [11] and Vlaar et al [7] both found a correlation between increased CPB time, surgical time and cross clamp time (Vlaar et al [7]) and the occurrence of "possible TRALI" .

Outcome

In our study, there was no increase in duration of ventilation or ICU stay for the " possible TRALI" patients. In Zah-Bogović et al`s [11] study, the patients had significantly increased ICU stay . Vlaar et al [7] found that the "possible TRALI" patients has significantly longer ventilation time, longer ICU and hospital stay. This was consistent with Gajic O et al [12] and Rana R et al [10]. Our patients not having any other risk factor for ALI in conjunction with comparable bypass time can be the reason

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why we had no increase in ventilation or ICU stay. There was no mortality in both the groups similar to the study done by Zah-Bogović [11] et al. Vlaar et al [7] in their study had a mortality of 13% for those who developed "possible TRALI" compared to the overall mortality of 4% in all cardiac surgery patients. In the study by Rana R et al [10] the mortality for the "possible TRALI " group was 71%. In the study by Gajic O et al [12] the mortaliy was 32%. The higher mortality in these studies was probably because the studies were done on critically ill patients who had other risk factors for lung injury. These patients also received more plasma rich products which have been implicated to cause the more severe form of TRALI [9]. Koch CG et al [14] found that there was increased morbidity and mortality associated with platelet, FFP and RBC transfusion in post-CABG patients. Wallis J P et al [16] observed that the mortality was 45%.

Our study had some limitatations. The diagnosis of TRALI was made on a clinical and radiological basis. The confirmatory diagnosis of TRALI is based on serological tests. These tests are not done in our institution and hence not available for this study. Because we chose electively mechanically ventilated patients, mild cases of TRALI that did not require ventilation might have been missed out. Hence this may have led to an under recognition and a lower incidence. These results are from a single center cardiothoracic ICU in a tertiary care hospital. There is a lack of data from other hospitals in India. In order to establish the actual incidence, larger multicenter studies should be conducted.

CONCLUSION:

The incidence of possible TRALI is high (5.4%) in patients who underwent CABG under CPB. The occurrence of TRALI is highest for platelet transfusion. A high index of suspicion for TRALI should be kept in mind in any patient who manifests clinical signs or symptoms within 6 hours of transfusion. Identifying these patients is vital and effective surveillance systems must be incorporated in order to establish increased awareness.

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