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Transfusion-related acute lung injury (TRALI)

Putu Dewi Pradnya Ardhaneswari[1*], Ni Nyoman Mahartini[2]

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[1]Study Program of Clinical Pathology, Faculty of Medicine, Universitas Udayana, Denpasar, Bali, Indonesia;
[2]Department of Clinical Pathology, Faculty of Medicine, Universitas Udayana, Prof. Dr. I.G.N.G Ngoerah General Hospital, Denpasar, Bali, Indonesia.

*Corresponding author:
Putu Dewi Pradnya Ardhaneswari;
Study Program of Clinical Pathology, Faculty of Medicine, Universitas Udayana, Denpasar, Bali, Indonesia;
pradnyadewii@yahoo.com

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ABSTRACT

After a transfusion, a clinical phenomenon known as transfusion-related acute lung injury (TRALI) manifests as acute hypoxia and noncardiogenic pulmonary edema. The onset of TRALI is usually 6 hours post-transfusion. Fresh Frozen Plasma (FFP) transfusion is the most frequent cause of TRALI. About 60% of critically sick patients died due to TRALI, and the expected mortality rate is between 5% and 8%.

TRALI's mechanism is not completely understood. In the antibody-mediated method, antigen-antibody binding to the recipient neutrophils results via the passive transfer of leuko-agglutinating antibodies through plasma in blood components. A second process results from the transfusion of biologically active substances like lipids, cytokines, or antibodies that leuko-agglutinate. This process will activate the neutrophils in the endothelium and cause the withdrawal of reactive oxygen species (ROS) and proteases. It can cause pulmonary capillary leakage, pulmonary edema, and TRALI.

TRALI is characterized by symptoms such as dyspnea, cyanosis, hypotension, tachycardia, fever, cough, and pulmonary edema. The complete blood count (CBC) usually shows leukocytosis, although it is often preceded by leukopenia. The serological examinations to support TRALI are Human Leukocyte Antigen class II (HLA-II) and neutrophils-specific antibodies.

Several differential diagnoses for TRALI include Transfusion-Associated Circulatory Overload (TACO), Acute Respiratory Distress Syndrome (ARDS), transfusion reactions due to anaphylactic shock, fluid overload, and bacterial contamination. Patients with TRALI's prognosis depends on the resolution of the hypoxemic state.

Keywords: anti HNA, FFP, leuko-agglutinating antibody, TRALI.
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INTRODUCTION

After a transfusion, a clinical phenomenon known as transfusion-related acute lung injury (TRALI) manifests as acute hypoxia and noncardiogenic pulmonary edema. TRALI is one of the transfusion complications related to acute lung injury. Damage to the capillary and alveolar membranes is induced by an immune-mediated interaction between leukocyte antibodies and leukocyte antigens.[1] Because TRALI seldom affects patients who get blood transfusions, including all types of blood products, red blood cells (RBC), fresh frozen plasma (FFP), and platelets (PLT), it is classified as a deadly syndrome. Lung damage that appears within 6 hours following a blood transfusion is known as TRALI.[2]

TRALI is undiagnosed and underreported in developing countries due to a lack of knowledge about TRALI. The differential diagnosis of TRALI includes acute pulmonary edema due to excess fluid or left ventricular failure and Acute Respiratory Distress Syndrome (ARDS). TRALI and ARDS are difficult to distinguish because they have the same symptoms.[2] Based on reports from the Food and Drug Administration (FDA), TRALI is most frequently caused by FFP transfusion. The prevalence of TRALI varies by patient population, and it is more common in patients who are severely ill. 60% of critically ill patients pass away with TRALI, which has an estimated fatality rate of 5 to 8%.[2,3]

According to the Quebec Hemovigilance program, the incidence of TRALI varies according to the type of blood component used. In 2007 TRALI was found in 1 case from 15,924 FFP transfusions, 1 case from 44,092 packed red cell (PRC) transfusions, 1 case from 40,452 whole blood (WB) transfusions, and 1 case from 47,000 platelet apheresis transfusions.[2,3] This review aims to synthesize the current information about TRALI.

METHODS

This study is a literature review. The primary literature sources were selected from PubMed and Google Scholar databases. A summary of the theory, research findings, and more research materials gathered from reference sources are included in the literature review, which serves as the foundation for future TRALI research.

RESULTS AND DISCUSSION

Risk Factors of TRALI

Recipient and transfusion risk factors are two categories of TRALI risk factors. Numerous comorbidities, such as end-stage liver disease, coronary artery bypass, hematological malignancy, large transfusion, mechanical ventilation, sepsis, multiparous pregnancy, and alcohol use, have been proposed as risk factors for TRALI in recipients or patients. A patient with a critical illness poses one of the greatest risks for TRALI. As the number

of transfusion units rises, the incidence of TRALI also rises.[4]

In case-control research, 89 patients with TRALI and 164 controls were enrolled to examine the transfusion procedure's risk variables. This study discovered that plasma from female donors was linked to a greater TRALI odds ratio (OR). TRALI incidence has been related to blood products with large plasma volumes, such as platelet concentrate, whole blood, and FFP. The risk of TRALI has been shown to rise with blood product age. RBC storage lesions are a variety of morphological and biochemical alterations caused by RBC storage.[5]

Pathophysiology of TRALI

TRALI's mechanism is not completely understood. According to the theory behind the antibody-mediated process, antigen-antibody binding to the recipient neutrophils results from the passive transmission of leuko-agglutinating antibodies through plasma carrying blood components. In the pulmonary capillaries, neutrophil aggregation is caused by antigen-antibody binding. It causes neutrophil activation, which in turn causes the release of neutrophil bioactive products, which consist of reactive oxygen species (ROS) and proteases that can cause capillary leakage, pulmonary edema, and TRALI by harming the pulmonary vascular endothelium. The antibodies are against Human Leukocyte Antigen (HLA) class I, HLA class II, and Human Neutrophil Antigen (HNA). Most of these antibodies were produced during pregnancy by multiparous women who received alloimmunization. In proportion to the number of parities, women's HLA class I and HLA class II antibodies will rise. Other non-immune mediators, such as the cluster of differentiation 40 (CD40) and various fats that accumulate during product storage can activate leukocytes in the lungs.[6,7]

Blood products with a high plasma content, such as FFP and platelets, are the blood components that most often cause TRALI. There are many antibodies in plasma products. However, TRALI can also be found in PRC transfusions.[7] Despite experimental and clinical data suggesting antibody-mediated TRALI, there are several issues with this idea, including:

1. Antibodies are not found in about 15% of cases.
2. Although HLA antibodies are frequently discovered in female donors, only a few result in TRALI.
3. Not all patients who receive transfusions from donors with HLA antibodies get TRALI.
4. Patients who suffer from TRALI do not always have antigens against leukocyte antibodies in the blood.

There are two hit mechanisms theories to answer this discrepancy. The two hit mechanisms hypothesis states that TRALI occurs due to two successive processes. The first process is a clinical condition with a predisposing factor, such as a severe infection, surgery and trauma. These circumstances will induce the pulmonary vascular endothelium to become activated, resulting in cytokine retention and an increase in adhesion molecules on the endothelial surface. The second method is the transfusion of physiologically active lipids, cytokines, and leuko-agglutinating antibodies. The activation of neutrophils within the endothelium as a result of this process will produce ROS and proteases, which can result in pulmonary capillary leakage, pulmonary edema, and TRALI. High levels of Vascular Endothelial Growth Factor (VEGF) or high levels of HLA II antibodies, which directly harm lung endothelial antigens, can both promote endothelial penetration and precipitate TRALI in neutropenic patients.[8]

Diagnosis and Clinical Features of TRALI

TRALI is characterized by symptoms such as dyspnea, cyanosis, hypotension, tachycardia, fever, cough, and pulmonary edema. The complete blood count usually shows leukocytosis, although it is often preceded by leukopenia. Symptoms appear within two to six hours after transfusion but can also develop up to 48 hours. In TRALI, severe pulmonary infiltration and hypoxia can persist for up to seven days.[8]

The TRALI criteria were established in 2004 by the US National Heart, Lung, and Blood Institute Working Group based on clinical and radiological findings split into three categories: suspected TRALI, possible TRALI, and delayed TRALI. The criteria for TRALI are shown in Table 1.[8]

Laboratory Examination For TRALI

Multiple cytokines and elevated plasma cytokines in TRALI patients are predictive indicators for patient prognosis. It's conceivable that cytokines found in blood derivatives induce TRALI directly. Leukocytes and platelets are the two sources of plasma cytokines that have been preserved. Inflammatory disease sufferers who do not exhibit any indications of inflammation at the time of donation can nonetheless produce cytokines. By reducing leukocytes, proinflammatory cytokines that build up in blood products can be eliminated.[6]

There are two reasons why TRALI is less common in leukocyte reduction products. First, TRALI is not caused by the reaction between the recipient antibody and donor leukocyte in the blood product. Second, reduction of leukocytes can reduce the accumulation of proinflammatory cytokines in blood products. Interleukin-8 (IL-8) and tumor necrosis factor alpha (TNF-alpha) are cytokines leukocytes can create while storing and accumulating in the plasma supernatant. IL-8 is crucial for promoting neutrophil activity in TRALI.[6]

TGF-1 is often linked to extracellular

Table 1. Criteria of TRALI[8]

Suspected TRALI
• Acute onset less than 6 hours after transfusion
• PaO2/FO2 <300 mmHg, or a worsening P to F ratio
• No signs of hydrostatic pulmonary edema (pulmonary arterial occlusion pressure <18 mm Hg or central venous pressure <15 mm Hg)
• Bilateral infiltrates on a lung X-ray
• There are no risk factors for acute lung injury
Possible TRALI
• Same as the criteria for suspected TRALI, but with risk factors for acute lung injury
Delayed TRALI
• Same as possible TRALI criteria where onset occurs 6-72 hours after transfusion

Table 2. Differential diagnosis of TRALI[1]

	TRALI	Anaphylactic reaction	Circulatory overload	Bacterial contamination
Respiratory Distress	• Lung edema caused by endothelial damage • Capillary leakage and tissue injury • Severe hypoxemia	Bronchospasm and laryngeal edema	Acute lung edema	Uncommon
Pulse rate	• Hypotension in 1-6 hours • Hypertension in 15% of cases	Hypotension in 1-45 minutes	• Acute hypotension • Usually with jugular vein distension	Hypotension in 1-2 hours
Temperature	Fever	No fever	No fever	Fever
Skin	Normal	Rash and redness	Edema	Redness
Diuretic treatment	No response		Response	
Blood component	• Plasma blood product • FFP	Blood component with plasma protein	All blood component	All blood product

substances in an inactive form. However, there is evidence of a correlation with TRALI. The amount of PAI-1 in the leukocyte reduced platelet product is unknown, but it is released by platelets. Recent studies have demonstrated that the CD40 surface molecule, recognized by the soluble CD40 ligand (sCD40L) molecule, is the mechanism by which neutrophil activation occurs. Platelet concentrations have a high sCD40L concentration.[8,9]

HLA class II and particular neutrophil antibodies are detected in the serological analysis of TRALI. It is advised to use flow cytometry and HLA-coated microbeads to find HLA antibodies in donor plasma. Combining the granulocyte agglutination test and the granulocyte immunofluorescence test can be used to detect neutrophil-specific antibodies.[6]

Differential Diagnosis of TRALI

Due to additional reasons, TRALI must be distinguished from pulmonary edema. Similar to TRALI, hemolytic and septic transfusion responses were observed. Like TRALI, anaphylaxis can result in respiratory insufficiency. However patients with anaphylaxis more frequently experience airway signs and symptoms. In patients with risk factors for ALI or ARDS, TRALI must be distinguished from acute lung injury (ALI) ARDS before transfusion.[10]

A transfusion reaction is known as TACO when it is accompanied by acute dyspnea from respiratory distress and acute pulmonary edema with diffuse bilateral infiltrates on a chest radiograph. One of the possible diagnoses for TRALI is TACO. The clinical features of TACO and TRALI are comparable. Fever and hypotension may be seen in TACO patients. Although TACO is not ruled out by normal fluid balance, it can happen in individuals who consumed a lot of fluid before the transfusion. Due to heart failure with a lower EF, patients with TACO may develop swollen neck veins and a reduced ejection fraction (EF). Due to elevated brain natriuretic peptide and cardiogenic pulmonary edema, the pulmonary artery occlusive pressure may be 18 mm Hg or more.[11]

Risk factors for TACO include intensive fluid treatment and impaired myocardial function. Fever, hypotension, and exudative lung infiltrates are among the signs and symptoms of inflammation more frequently linked to TRALI. Conversely, TACO was more commonly linked to symptoms that would point to heart dysfunction or volume overload.[1] Other differential diagnoses of TRALI can be ruled out by the criteria in Table 2.

Prognosis of TRALI

The mortality rate of TRALI is 5-10% and mortality less than 90 days associated with TRALI can be as high as 47% in the critical patient population. There are no late consequences, such as fibrosis or other structural damage to the lung parenchyma, and long-term lung function in patients with TRALI is comparable to that of persons who never had TRALI. The clinical outcome of TRALI patients is a result of the hypoxemia's quick recovery (around 2 days from the transfusion interval). Cases that may be TRALI-related should be reported right away to the blood bank. Blood banks can check for anti-HLA and anti-HNA antibodies in all connected donors.[6]

CONCLUSION

Acute hypoxia and noncardiogenic pulmonary edema during or after transfusion are the clinical symptoms of TRALI. TRALI's mechanism is not completely understood. The passive transfer of leuko-agglutinating antibodies through plasma-containing blood components is one route that results in antigen-antibody binding to the recipient neutrophils. Dyspnea, cyanosis, hypotension, tachycardia, fever, cough, and pulmonary edema are some of the symptoms that define TRALI. Neutrophil-specific antibodies and HLA class II are the serological tests that support TRALI. TRALI has TACO, ARDS, and transfusion responses brought on by anaphylactic shock, overload, and bacterial contamination in its differential diagnostic list. TRALI has a mortality rate of 5% to 10%. In the critically ill group, the 90-day mortality linked with TRALI might be as high as 47%. The TRALI patient's prognosis depends on how quickly the hypoxemic condition is resolved. To understand the outcomes of patients, more research is required in evaluating the TRALI consequences.

CONFLICT OF INTEREST

There are no conflicts of interest in this study, according to all the authors.

ETHICAL CONSIDERATIONS

Not applicable.

AUTHOR CONTRIBUTIONS

Each author made an equal number of contributions to this study.

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