Blood Reviews 29 (2015) 51–61

Contents lists available at ScienceDirect

Blood Reviews

journal homepage: www.elsevier.com/locate/blre

REVIEW

Pathogenesis of non-antibody mediated transfusion-related acute lung injury from bench to bedside

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ARTICLE INFO

Keywords:
TRALI
Storage
sCD40L
Duffy antigen
LysoPCs
Transfusion
Non-transferrin bound iron
Heme
microparticles
Red blood cells
Platelets

ABSTRACT

Transfusion-related acute lung injury (TRALI) is a major cause of transfusion-related mortality. Causative factors are divided in antibody mediated TRALI and non-antibody mediated TRALI. Antibody mediated TRALI is caused by passive transfusion of cognate antibodies and non-antibody mediated TRALI is caused by transfusion of aged cellular blood products. This review focuses on mechanisms in non-antibody mediated TRALI which includes soluble mediators accumulating during storage of red blood cells (RBCs) and platelets (PLTs), as well as changes in morphology and function of aged PLTs and RBCs. These mediators cause TRALI in two-hit animal models and have been implicated in TRALI onset in clinical studies. Pre-clinical studies show a clear relation between TRALI and increased storage time of cellular blood products. Observational clinical studies however report conflicting data. Knowledge of pathophysiological mechanisms of TRALI is necessary to improve storage conditions of blood products, develop prevention strategies and develop a therapy for TRALI.

1. Introduction

Transfusion-related acute lung injury (TRALI), a syndrome of respiratory distress caused by transfusion of blood products, is a major cause of transfusion-related mortality [1–4]. In the absence of biomarkers, TRALI is defined according to the TRALI conference and US National Heart, Lung and Blood Institute definition as onset of acute lung injury within 6 h of blood transfusion without an additional risk factor for acute lung injury (Table 1) [2,3,5]. Patients suffering TRALI develop symptoms of dyspnea, fever, hypotension and sometimes hypertension, hypoxia, passing leukopenia, thrombopenia and bilateral infiltrates on chest X-ray. Typical post-mortem findings in the lung of patients who die of TRALI are pulmonary edema, diffuse alveolar damage, hyaline membrane formation and extensive granulocyte infiltration and aggregation in the alveoli [6,7]. TRALI incidence varies between 0.08–15.1% per patient transfused and 0.01–1.12% per product transfused. Critically ill patients bear an increased risk for developing TRALI after blood transfusion [8,9]. The high incidence of TRALI in critically ill patients can be explained in light of the "two-hit hypothesis": a "first hit", an underlying clinical condition of the patient, causes priming of the pulmonary neutrophil. The "second hit", the transfusion of a cellular blood product, causes activation of the neutrophils in the pulmonary compartment resulting in TRALI. Hematological malignancy, cardiovascular disease, sepsis, fluid overload, emergency cardiac surgery, massive transfusion, mechanical ventilation, high APACHE-II score, increasing age, shock, alcohol dependence kidney failure and severe liver disease have been identified as risk factors for a "first hit" [8,10–14]. Originally, infusion of cognate donor antibodies of the human leucocyte antigens (HLA) and human neutrophil alloantigen (HNA) was recognized as causative factor in TRALI. In these cases antigen–antibody interaction led to activation of primed neutrophils, so called antibody-mediated TRALI [15,16]. However, antibodies are not involved in all cases fulfilling the clinical definition of TRALI [17–19] and recipients of a product which contains antibodies do not always develop TRALI, even in the presence of the cognate antigen [20]. This resulted in the hypothesis of non-antibody mediated TRALI. The causative agent in non-antibody mediated TRALI is still unknown. Several mechanisms have been proposed in which accumulation of cell derived substances in donor blood and storage related changes of the donor red blood cells (RBCs) and donor platelets (PLTs) cause TRALI [18]. This review summarizes evidence on the pathogenesis of non-antibody-mediated TRALI from both preclinical and clinical studies. Given the association between TRALI and adverse outcome in several patient populations [13,21], identification of causative factors is paramount to develop prevention and treatment strategies for TRALI. Knowledge of pathophysiological mechanisms of TRALI

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http://dx.doi.org/10.1016/j.blre.2014.09.007
0268-960X/

Table 1
Definition transfusion-related acute lung injury (TRALI) according to the TRALI conference and US National Heart, Lung and Blood Institute Definition [2,3,5].

Suspected TRALI	Acute onset within 6 h of blood transfusion $PaO_2/FI\ O_2$ < 300 mm Hg, or worsening of P to F ratio Bilateral infiltrative changes on chest radiograph No sign of hydrostatic pulmonary edema (pulmonary arterial occlusion pressure ≤18 mm Hg or central venous pressure ≤15 mm Hg) No other risk factor for acute lung injury
Possible TRALI	Same as for suspected TRALI, but another risk factor present for acute lung injury
Delayed TRALI	Same as for (possible) TRALI and onset within 6–72 h of blood transfusion

is necessary to improve storage conditions of blood products and refine transfusion policies.

2. Methods

Embase and PubMed were accessed for relevant English literature. Search strategy for PubMed was ((((transfusion-related acute lung injury[tw] OR TRALI[tw])) OR (("Acute Lung Injury"[MeSH]) AND ("Blood Transfusion"[Mesh] OR transfusion[tw])))) AND ("Models, Animal"[Mesh] OR animal model * [tw] OR "Cohort Studies"[MeSH Terms] OR cohort[tiab] OR "Humans"[MeSH] OR "Animals"[Mesh]) and keywords in Embase "Transfusion-related lung injury", "TRALI", "animal", "cohort analysis" and "human". Articles were selected based on title and abstract. References of all relevant articles were checked and included when considered relevant. Conference abstracts were excluded.

3. Pathogenesis non-antibody mediated TRALI

The current understanding of the pathogenesis of non-antibody mediated TRALI suggests it is caused by transfusion of a stored cellular blood product in the presence of a "first hit". A second hit then induces lung injury [22]. This is in contrast with antibody mediated TRALI in which majority of TRALI cases are related to cognate antibodies in plasma containing transfusion products. In short, TRALI is thought to be mediated by neutrophils [23]. Pulmonary endothelium release cytokines and chemokines which facilitate neutrophil migration to the lung. There, L-selectin mediates loose binding of the neutrophil on the epithelium after which firm adhesion is mediated by E-selectin, platelet-derived P-selectin and intracellular adhesion molecules (ICAM-1). The transfusion product activates these neutrophils and lung injury develops. The neutrophils adhere to the injured capillary endothelium and migrate into the air space where they release oxidants, proteases, platelet-activating factor (PAF) and neutrophil extracellular traps (NETs). The air space is filled with protein-rich oedema and cytokines interleukin-1, -6, and -8, (IL-1, IL-6, and IL-8, respectively). These stimulate chemotaxis and stimulate neutrophils to form elastase-α1-antitrypsin (EA) complex. The clinical symptoms of acute respiratory distress is caused by influx of protein-rich oedema into the alveolus which leads to the inactivation of surfactant (Fig. 1) [9,24,25]. Possibly symptoms of acute lung injury are not only caused by release of proteases by activated neutrophils, but also by ischemic lung damage as an effect of platelet aggregation in the pulmonary capillaries. Of interest neutrophil deficient patients also have been described to develop TRALI [26] and histochemical coloring of lung sections of patients who died of TRALI do not always show neutrophil influx in the alveolar space [27]. The past years research has focused on pro-inflammatory mediators which accumulate in stored cell containing blood that serve as a "second hit". More recent the transfused aged red blood cell (RBC) and platelet (PLT) themselves have been implicated as well in the onset of TRALI [13,28].

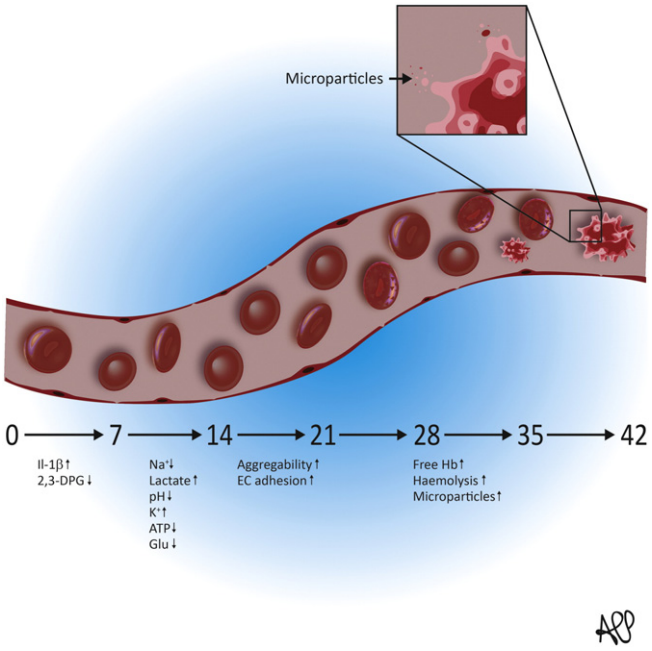

Fig. 1. Pathophysiology of transfusion-related acute lung injury (TRALI). A "first hit", an underlying clinical condition of the patient, results in priming of neutrophils and attracting them to the lung capillary by release of cytokines and chemokines by lung endothelium. L-selectin loosely binds the neutrophils after which E-selectin, platelet-derived P-selectin and intracellular adhesion molecules (ICAM-1) facilitate firm adhesion. The "second hit", the transfusion of a blood product, causes activation of the neutrophils resulting in TRALI. Neutrophil activation results in neutrophils margination through the interstitium into the alveoli which are filled with protein-rich edema. Here, cytokines, interleukine-1β, -6, -8 (Il-1β, Il-6, Il-8) are secreted which further stimulate neutrophil chemotaxis and neutrophil formation of elastase-α1-antitrypsin (EA) complex. Increase in thrombin-antithrombin complexes (TATc) and reduction of plasminogen activator activity (PAA) indicate activation of coagulation. The "second hit", the transfusion product may contain accumulated bioactive lipids (BAL), soluble CD40 ligand (sCD40L), aged RBCs with reduced levels of Duffy antigen or UV-B illuminated platelets. Hypothesized mediators are microparticles (MP), non-transferrin bound iron and aged RBCs or platelets. RBCs: red blood cells; PLTs: platelets. PAI: plasminogen activator inhibitor.

3.1. Recent insights in TRALI pathogenesis

The role of hemin and neutrophil extracellular traps (NETs) has recently been related to TRALI pathogenesis. Hemin is iron-containing protoporphyrin IX. It is essential for the formation of heme-containing proteins including hemoglobin, myoglobin, nitric oxide synthases and cytochromes. Hemin can be released under various pathological conditions as β-thalassemia, glucose-6-phosphate dehydrogenase deficiency, hemorrhage, hemolysis and muscle injury. An excess of free circulating hemin can results in formation of reactive oxygen species and cellular injury [29]. NETs can be released by activated neutrophils to trap pathogens and thus prevent pathogen spreading [30]. They are composed of DNA fibers decorated with histones and antimicrobial proteins. Their formation follows a specific pattern of histone hypercitrullination, chromatin decondensation, dissolution of granular and nuclear membranes and cytolysis. Although NETs have been associated with beneficial antimicrobial function by trapping gram − negative and gram + positive bacteria [30], they also have been related to amongst others colitis ulcerosa [31], small-vessel vasculitis [32] and preeclampsia [33]. Recently NETs have been detected in the circulation of patients with TRALI [34]. To determine whether these were causative or consequence in TRALI the effect of NETS have been studied *in vitro*. *In vitro* NETs induce enhanced permeability in primed human umbilical vein endothelial cells (HUVECs) [35] and NETs were found in two TRALI mouse models. In these *in vivo* models mice were primed with LPS after which infusion of MHC-I antibody functioned as "second hit". Mice