Coagulopathy and plasma transfusion in critically ill patients

Müller, M.C.A.

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Risk factors for transfusion-related acute lung injury in ICU patients

Marcella C.A. Müller, Nicole P. Juffermans

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Chapter 10

Introduction

Multiple observational studies have shown an association between transfusion and lung injury in the critically ill [1-6]. The definition of transfusion-related acute lung injury (TRALI) is the onset of acute lung injury (ALI) occurring within 6 hours following a blood transfusion. When other risk factors for ALI are present, the term ‘possible TRALI’ is used [7,8]. Although a temporal relation with a blood transfusion is an obvious requirement for the definition of TRALI, the time frame of 6 hours is arbitrarily chosen. Indeed, it has been recognized that transfusion can result in delayed respiratory complications, termed ‘delayed TRALI syndrome’ [9].

Recent observational studies suggest that the incidence of TRALI is high in several critically ill risk populations. Cohort studies in critically ill patients report a 100-fold higher incidence of TRALI when compared to the general hospital population [10,11]. Of note, the attributive morbidity and mortality of TRALI is considerable. Up to 70% of patients who develop TRALI needs referral to the intensive care unit (ICU) and invasive mechanical ventilation [12]. When TRALI develops in patients already admitted to the ICU, there is an association with prolonged mechanical ventilation, increased hospital mortality and a decreased long-term survival [10,11,13]. Prognosis of the ‘delayed TRALI syndrome’ is particularly bad, with an estimated mortality of 40% [9].

Obviously, blood transfusion cannot be avoided altogether. The high incidence and considerable morbidity and mortality of TRALI warrant insight in the risks and benefits of the decision to administer a blood transfusion. This chapter aims to address the susceptibility of critically ill patients to the development of a TRALI reaction. Risk factors for critically ill patients to develop TRALI as well product-related risk factors will be discussed. Efforts to reduce TRALI have focused to date on modification of blood products, which has resulted in a substantial reduction in TRALI cases, but has not completely mitigated TRALI. In this chapter, we suggest that complete mitigation requires physicians to develop new approaches for patient-specific transfusion practice, aimed at pre-emptively taking action to decrease the risk of TRALI. It may be time to improve our assessment of the critically ill patient in need of a transfusion.
Pathogenesis of TRALI

The high incidence of TRALI reported in critically ill patient populations may be a consequence of its pathogenesis. TRALI is mediated by the interaction of neutrophils with pulmonary endothelial cells and can be caused by any cell-containing or plasma rich blood product. TRALI is thought to occur as a result of a ‘two hit’ insult [14,15]. The first ‘hit’ is an inflammatory condition of the patient at the time of the transfusion (e.g. sepsis, recent surgery), causing sequestration and priming of neutrophils and the expression of adhesion molecules in the pulmonary compartment. In response to priming, neutrophils undergo changes allowing for close contact with the endothelial surface of the pulmonary vasculature. The second ‘hit’ is mediated by components in the transfusion product. Donor antibodies against human neutrophil antigens (HNA) or human leukocyte antigens (HLA) present on leukocytes in the lungs of the recipient have been implicated. Also bioactive substances that have accumulated during blood storage may play a role in TRALI. These mediators are thought to stimulate the primed neutrophils to release proteases resulting in endothelial damage, vascular permeability and the full clinical picture of TRALI [16,17].

Findings from experimental models support the assumption that in TRALI, neutrophils are primed by inflammation. Priming with a ‘first hit’ of endotoxin (LPS) was found to be a prerequisite for induction of TRALI using plasma from stored blood products [16-19]. In the presence of a priming ‘hit’, it was demonstrated that lower amounts of antibody were sufficient to elicit the TRALI reaction [20], which supports the notion that the presence of an inflammatory response increases susceptibility to TRALI. Thereby, both transfusion and patient-related factors play a role in TRALI pathogenesis.

Blood product-related risk factors for TRALI

Anti-leukocyte antibodies

From case series, the presence of donor anti-leukocyte antibodies in the transfused product is thought to be implicated in TRALI. Involved antibodies are mainly directed against HLA Class I, HLA Class II or HNA. Activation of neutrophils occurs
via HLA Class I antigens. Mononuclear cells expressing HLA Class II are involved by activation through HLA Class II antibodies [21]. Recently, a large, prospective, case-controlled multicenter study systematically identified factors associated with an increased risk of TRALI [22]. In this study, blood product-related risk factors were the transfused volume of high titer cognate HLA class II antibody and the volume of high titer HNA antibody. Antibodies not associated with increased risk of TRALI were non-cognate or weak anti-HLA class II antibody, as well as HLA class I antibodies. The finding that the presence of HLA Class II antibodies in plasma of blood donors was of greater importance then class I, underlines results from previous studies [23]. Antibodies against the HNA-3a or 5b antigen appear to be especially important in causing severe cases of TRALI [24].

**Bioactive response modifiers**

Bioactive lipids (lysoPCs and neutral lipids) increase during storage of red blood cells (RBCs) and platelet concentrates [25,26]. These substances were shown to have in vitreo neutrophil priming capacity and can induce TRALI in animal models [16-18]. A retrospective clinical study of 10 TRALI patients linked the occurrence of TRALI with transfusion of blood products containing lipids with neutrophil-priming activity [27]. However, this finding was not confirmed in a study in cardiac surgery patients developing TRALI [28]. Also, in the largest prospective case-control study to date, no association was found between bioactive lipids and TRALI [22]. Other bioactive substances, such as pro-inflammatory cytokines, have not been consistently linked to TRALI [22].

**The red cell storage lesion**

During storage, RBC products undergo changes that affect their function and in vivo survival, which are collectively termed the “storage lesion”. *In vitro* experiments have shown increased reactive oxygen species (ROS) formation by endothelial cells upon incubation with aged red blood cells but not with fresh cells [29]. Indeed, in a murine “two hit” transfusion model, aged RBCs were capable of inducing a TRALI reaction [30]. The proposed mechanism is either a decrease in the chemokine scavenging function of the RBC [31] or increased adhesion of the erythrocyte to the endothelium due to a deficiency of anti-adhesive adenosine-5’-triphosphate release
from the RBC [32]. Hereby, transfused RBCs may promote or exacerbate microvascular pathophysiology in the lung.

In conclusion, cognate HLA class II antibodies are blood product-related risk factors for TRALI. Bioactive lipids can function as a second ‘hit’ and are able to induce a TRALI reaction, but clinical data are conflicting. The aged RBC seems to play a role in preclinical models of TRALI. To date, interventions aimed at decreasing TRALI incidence have focused on product-related risk factors.

Mitigating TRALI by modifying blood products

Exclusion of female donors
The prevalence of anti-leukocyte antibodies in the donor population depends on donor allo-exposure. Transfusion can lead to sensitization of recipients, albeit with very different reported numbers, ranging from 1 to 12% [33]. However, pregnancy is the most important cause of sensitization in the donor population. Approximately 10% of previously pregnant women have HLA antibodies and this number increases to 26-39% in women who have had three or more pregnancies [33]. In order to prevent antibody mediated TRALI, a predominantly male donor strategy for preparation of plasma rich products (including fresh frozen plasma and buffy coat-derived pool platelets) was first implemented in the United Kingdom in 2003. Other countries followed. This resulted in a ~70% reduction in reported TRALI cases [33-37]. Hence, it seems that exclusion of female plasma donors prevents the majority of TRALI cases caused by plasma-rich products. However, TRALI cases that occur due to RBC transfusion and pooled platelets are not prevented.

Transfusion of fresh red blood cells only
The accumulation of compounds, such as bioactive lipids, during storage suggests that the occurrence of TRALI may be associated with the use of older blood. A meta-analysis of studies on the effect of transfusion of stored blood showed an association between transfusion of stored blood and mortality in various patient populations [38]. In cardiac surgery patients, an association of prolonged storage of blood products and lung injury was found [39]. However, a large prospective study did not find
evidence for an association between red cell storage duration and TRALI [22]. In a prospective case-control study in ICU patients, stored red blood cell products did not have any effect on pulmonary function or gas exchange [40]. Prospective randomized controlled clinical trials investigating the effect of fresh compared to stored RBCs on outcome in the critically ill are currently underway.

Patient-related risk factors for TRALI

Predisposing factors for TRALI presumably lower the recipient’s threshold for developing TRALI. Specific host factors have recently been identified (table 1). In a mouse model of TRALI, mechanical ventilation synergistically augmented lung injury, which was even further enhanced by the use of injurious ventilator settings [41], supporting the concept that mechanical ventilation aggravates the course of a TRALI reaction. There are also clinical data suggesting that mechanical ventilation may be a risk factor for lung injury following blood transfusion. As much as 33% of mechanically ventilated critically ill patients develop lung injury within 48 hours after transfusion in an observational study [3]. In accordance, it was found that the presence of mechanical ventilation predisposed to acquiring TRALI in a retrospective study in ICU patients [11]. Furthermore, a recent study confirmed that high peak airway pressures (>30 cm H₂O) contributed to an increased TRALI risk (OR 5.6 [2.1-14.9]) [22].

In addition to pulmonary hits, systemic inflammatory conditions are often present in critically ill patients. In a retrospective study on risk factors for TRALI in ICU patients, 87% of the patients that confirmed to the diagnostic criteria for TRALI had a risk factor for ALI prior to onset of (possible) TRALI [11]. Hence, it is not surprising that there is an overlap between risk factors for ALI and TRALI. Of note, comparable to possible TRALI, ALI is a syndrome which occurs as a complication of an inflammatory condition.

Sepsis has been identified as a risk factor for TRALI in several studies in ICU patients [10,11]. This is in line with animal models showing that endotoxemia reduceds the amount of antibodies or bioactive response modifiers needed to induce TRALI [16,20]. The presence of shock prior to transfusion increased TRALI risk [22]. Of interest, plasma interleukin (IL)-8 levels in TRALI patients on a general hospital ward were elevated prior to transfusion, underlining the contribution of an inflammatory
status to the risk of developing TRALI [22]. In cardiac surgery patients prospectively followed for the onset of TRALI, IL-8 levels prior to transfusion were elevated compared to transfused controls [42]. Because IL-8 has neutrophil-priming capacity, we hypothesize that during an insult, endothelial cells produce IL-8, contributing to attraction of neutrophils to the pulmonary compartment [42]. Whether IL-8 can serve as a biomarker for diagnosing TRALI remains to be determined.

Coronary artery bypass grafting (CABG) was found to be a risk factor for TRALI [11,43]. In this context, the incidence of TRALI was found to be 2.4% in a prospective study in cardiac surgery patients [28], which is about 8 to 10-fold higher compared to the general patient population. We speculate that this may be due to a longer time on cardiopulmonary bypass (CPB) [28]. Hematologic malignancy is also a TRALI risk factor in a general hospital patient populations as well as in ICU patients [11,43]. Massive transfusion is a risk factor for acute respiratory distress syndrome (ARDS) [1,4] as well as for TRALI [11]. In patients admitted to the ICU because of bleeding, the presence of liver failure was a strong risk factor for developing TRALI when compared to transfused patients without liver failure [13]. It is not clear whether these conditions are risk factors solely because these patients commonly receive multiple transfusions, or that fluid overload induces priming. Of note, a prospective case control study in TRALI patients in the general hospital population revealed that an increased TRALI risk was associated with a positive fluid balance [22]. This is in line with findings in ALI patients [44] and indeed suggests that fluid overload may play role in TRALI pathogenesis.

Taken together, critical illness contributes to increased susceptibility to a TRALI reaction. Of note, in a multivariate analysis of a retrospective study in ICU patients, patient-related risk factors were more important for the onset of TRALI than transfusion-related risk factors, suggesting that development of a TRALI reaction depends more on host factors then on factors in the blood product [11]. This finding suggests that taking an active approach in daily ICU practice may be effective in mitigating the risk of TRALI.
### Table 1: Patient-related risk factors for transfusion-related acute lung injury (TRALI)

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Author, date [ref]</th>
<th>Type of study</th>
<th>Relation between risk factor and TRALI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sepsis</td>
<td>Rana, 2006 [46]</td>
<td>Retrospective case control</td>
<td>Sepsis in 48% TRALI patients (p&lt;0.01 vs. controls)</td>
</tr>
<tr>
<td></td>
<td>Gajic, 2007 [10]</td>
<td>Prospective case control</td>
<td>Sepsis in 37% patients developing lung injury after transfusion (p=0.016 vs. controls)</td>
</tr>
<tr>
<td></td>
<td>Vlaar, 2010 [11]</td>
<td>Retrospective cohort</td>
<td>Sepsis predisposes to TRALI (OR 2.5 [1.2-5.2])</td>
</tr>
<tr>
<td>Shock</td>
<td>Toy, 2012 [22]</td>
<td>Prospective case control</td>
<td>Shock prior to transfusion predisposes to TRALI (OR 4.2 [1.7-10.6])</td>
</tr>
<tr>
<td>Mechanical ventilation</td>
<td>Gajic, 2004 [3]</td>
<td>Retrospective cohort</td>
<td>33% of ventilated patients develop lung injury within 48 hours after transfusion</td>
</tr>
<tr>
<td></td>
<td>Vlaar, 2010 [11]</td>
<td>Retrospective cohort</td>
<td>Mechanical ventilation predisposes to TRALI (OR 3.0 [1.3-7.1])</td>
</tr>
<tr>
<td></td>
<td>Toy, 2012 [22]</td>
<td>Prospective case control</td>
<td>Peak airway pressure of &gt;30 cm H₂O predisposes to TRALI (OR 5.6 [2.1-14.9])</td>
</tr>
<tr>
<td>Cardiac surgery</td>
<td>Vlaar, 2010 [11]</td>
<td>Retrospective cohort</td>
<td>Emergency cardiac surgery predisposes to TRALI (OR 17.6 [1.8-168.5])</td>
</tr>
<tr>
<td></td>
<td>Toy, 2012 [22]</td>
<td>Prospective case control</td>
<td>Cardiac surgery predisposes to TRALI (OR 3.3 [1.21-9.2])</td>
</tr>
<tr>
<td></td>
<td>Vlaar, 2011 [28]</td>
<td>Prospective case control</td>
<td>Time on cardiopulmonary bypass predisposes to TRALI (OR 1.0 [1.0-1.03])</td>
</tr>
<tr>
<td>Hematologic malignancy</td>
<td>Rana, 2006 [46]</td>
<td>Retrospective case control</td>
<td>Hematologic malignancy in 25% TRALI patients (p&lt;0.01 vs. controls)</td>
</tr>
<tr>
<td></td>
<td>Silliman, 2003 [43]</td>
<td>Retrospective cohort</td>
<td>Hematologic malignancy in 46% of TRALI patients (p=0.0004 vs. transfused controls)</td>
</tr>
<tr>
<td>Positive fluid balance</td>
<td>Toy, 2012 [22]</td>
<td>Prospective case control</td>
<td>Fluid balance, increment per liter, predisposes to TRALI (OR 1.17 [1.08-1.28], p&lt;0.001)</td>
</tr>
<tr>
<td>Liver failure</td>
<td>Benson, 2010 [13]</td>
<td>Retrospective cohort</td>
<td>Liver failure predisposes to TRALI (OR 13.1 [2.7-63.8])</td>
</tr>
<tr>
<td></td>
<td>Toy, 2012 [22]</td>
<td>Prospective case control</td>
<td>Liver transplant surgery predisposes to TRALI (OR 6.7 [1.3-35.7])</td>
</tr>
</tbody>
</table>

Data are percentages or odds ratio (OR) with confidence interval
Mitigating TRALI by individualized patient intervention

Appropriate management of critically ill patients has decreased their risk of developing ALI. The same may hold true for TRALI. Given the high number of ICU patients who receive a blood transfusion, the association between blood transfusion and adverse outcome in the critically ill [10,11,13] and the recent identification of TRALI risk factors, it is possible and perhaps even mandatory for ICU physicians to take an individualized approach towards their patients in need of a transfusion. Patient-focused strategies that may decrease the risk of TRALI include: monitoring fluid balance; shock prior to transfusion should be avoided; a restrictive fluid balance should be maintained. Decreasing airway pressures in patients on mechanical ventilation prior to transfusion may also decrease the risk of TRALI. Although not proven in clinical trials, low tidal volume ventilation may further reduce TRALI risk. With the use of electronic medical records, protocols can be developed to further decrease the risk of TRALI. An electronic screening algorithm has been developed which accurately identifies TRALI patients [45]. Improvement in identification may contribute to better patient management of a TRALI case. Electronic health record surveillance may also be a tool for further implementing measures to decrease TRALI.

Conclusion

The presence of an inflammatory condition increases the susceptibility to TRALI. Specific patient-related risk factors have been identified, empowering the ICU physician to take an individualized approach to the patient in need of a transfusion, which may contribute to mitigating the risk of TRALI.
References