Transfusion-Related Acute Lung Injury: Incidence, Pathogenesis and the Role of Multicomponent Apheresis in Its Prevention

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Key Words

Transfusion-related acute lung injury ·
Multicomponent collection · Apheresis

Summary

Although transfusion-related acute lung injury (TRALI) is now appreciated as the most common cause of death from transfusion, its incidence remains unknown. The most frequently cited figure is 1:5,000 plasma-containing components. Certain patient groups may be at significantly higher risk. TRALI is both underdiagnosed and underreported. It is misdiagnosed as transfusion-associated circulatory overload. Several mechanisms have been proposed for its pathogenesis – leukocyte antibodies and the 2-hit model. These may overlap, and both involve transfusion of leukocyte antibodies. Passive transfusion of leukocyte antibodies is strongly associated with TRALI; these are identified in 60–85% of cases. Multiparous blood donors are the most frequent source of these antibody-containing components. The antibodies are HLA class I and II and/or granulocyte-specific. In 50% of cases the antibody corresponds to an epitope in the patient. HLA class I antibodies have been shown to prime and activate neutrophils. Clinical reports and animal models link HNA-3a antibodies with severe lung injury. A number of TRALI prevention and risk mitigation strategies have been proposed. In the UK and the USA, these strategies have centered upon excluding 'high risk' (HLA/HNA antibody containing) plasma from fresh frozen plasma and platelet products. Multicomponent apheresis collection of platelets, plasma and red blood cells is a means of accomplishing this objective.

Schlüsselwörter

Transfusionsassoziierte akute Lungeninsuffizienz ·
Multikomponentenspende · Apherese

Zusammenfassung

Obwohl die transfusionsassoziierte akute Lungeninsuffizienz (TRALI) mittlerweile als die häufigste Ursache für transfusionsbedingte Todesfälle eingeschätzt wird, ist ihre Inzidenz nicht bekannt. Die am häufigsten zitierte Zahl in diesem Zusammenhang ist 1 pro 5000 Plasma enthaltende Komponenten. Bestimmte Patientengruppen haben vermutlich ein signifikant höheres Risiko. TRALI wird einerseits oft nicht erkannt, andererseits wird zu selten darüber berichtet. Sie wird als transfusionsassoziierte Kreislaufüberlastung fehldiagnostiziert. Als pathogenetische Mechanismen wurden bisher Leukozytenantikörper und das 2-Hit-Modell prognostiziert. Möglicherweise gibt es auch eine Überlagerung dieser beiden Mechanismen – beide schließen die Transfusion von Leukozytenantikörpern ein. Eine passive Transfusion von Leukozytenantikörpern ist eindeutig mit TRALI assoziiert, sie kann in 60–85% der Fälle nachgewiesen werden. Komponenten, die Antikörper enthalten, stammen meist von multiparen Blutspendern. Die Antikörper sind HLA-Klasse-1- und -2- und/oder granulozytenspezifisch. In 50% der Fälle korrespondiert der Antikörper mit einem Epitop des Patienten. Für HLA-Klasse-1-Antikörper wurde gezeigt, dass sie Primer für Neutrophile sind und diese aktivieren. Klinische Reports und Tiermodelle zeigen eine Verbindung von HNA-3a-Antikörpern und schwerer Lungeninsuffizienz. Eine Reihe von TRALI-Vermeidungs- und -Risikominimierungsstrategien wurde bereits vorgeschlagen: In Großbritannien und den USA konzentrieren sich diese Strategien auf den Ausschluss von (HLA/HNA-Antikörper enthaltenden) Hochrisikoplasma aus frisch-gefrorenem Plasma und Thrombozytenprodukten. Die Multikomponenten-Apheresespende von Thrombozyten, Plasma und Erythrozyten ist ein weiterer Ansatz, mit diesem Problem umzugehen.

Incidence, Morbidity and Mortality

The incidence of transfusion-related acute lung injury (TRALI) is unknown. The reasons for this are manifold. These include the fact that prior to 2004 there was no standard clinical definition, lack of reliable denominator data, under-recognition and underreporting as well as confusion with other clinical entities, notably transfusion-associated circulatory overload (TACO) [1]. These factors account for the widely disparate figures that have been reported. From the USA two frequently cited studies found an incidence of 1 in 1,300 and 1 in 5,000 plasma-containing transfusions [2, 3]. At the Mayo Clinic, nurses specially trained in transfusion practice and reactions, are responsible for blood administration outside the operating room, providing a degree of vigilance not usually found. In a single-hospital report from the UK that addressed fresh frozen plasma (FFP) transfusions, the incidence was 1 in 7,900 units [4]. The most frequently implicated blood products are whole blood (WB), packed red blood cells (RBC), FFP, whole blood-derived platelets (PC) and apheresis platelets (SDP). From the Quebec Hemovigilance program, the incidence varies widely by blood component. In 2005 TRALI was found in 1 in 15,924 FFP, 1 in 44,092 RBC, 1 in 40,452 WB platelet pools, and 1 in 47,000 SDP [6]. Whether the differences in incidence for component types reflect the plasma volume or some intrinsic factors is unknown.

A recent nested control study of consecutive intensive care unit patients who did not require respiratory support prior to transfusion identified TRALI in 1:534 transfusions [7]. The same study found that TACO was identified in 1:356 components. This study would suggest that in certain clinical settings TRALI is common. A prospective study at two large medical centers found that TRALI occurred in 1:3,183 units and in 1:473 patients transfused [8]. Reports of the US Food and Drug Administration (FDA) of transfusion-associated deaths indicate an association with cardiovascular surgery, active infection and hematologic disease [9]. Others have linked massive transfusion, thrombotic thrombocytopenic purpura and surgical procedures [10]. Gajic et al. [11] reported that patients with acute lung injury were more likely to have sepsis and a history of chronic alcohol abuse. How any of these factors contribute to or precisely act as triggers for TRALI is unknown. TRALI cases are evenly distributed between males and females. TRALI has been identified in all age groups, including children and elderly patients [12]. A recent French hemovigilance report found that TRALI was more frequent in patients 60 years and older [13].

In a look-back study of 50 patients who received plasma from a donor known to have an HLA antibody, 7 mild or moderate reactions and 8 severe reactions were identified [14]. Severe reactions were defined as those requiring mechanical ventilation. Of these, only 2 reactions were reported to the transfusion service in the hospital. Repeat reactions in the same patient were also identified. This report provides insight as to

why an institution does not believe it has a TRALI 'problem'. TRALI is both underrecognized and underreported.

The clinical impact of the severe manifestations of TRALI is significant. In one of the earliest and largest series reported, Popovsky and Moore [3] found that of 36 patients with classic TRALI, each required supplemental oxygen. 72% were placed on mechanical ventilation. In 81% there was rapid clinical, physiologic and radiologic improvement, with resolution of the pulmonary infiltrates in 96 h or less. 17% of patients had a slower resolution of their pulmonary infiltrates, but unlike the adult respiratory distress syndrome (ARDS) caused by other etiologies (e.g., infection, toxins), the lung injury is reversible. If the patient survives the initial insult, there are no permanent sequelae. For this reason, distinguishing TRALI from ARDS is important.

Among immediate transfusion reactions, TRALI is singular in its mortality rate. Only hemolytic transfusion reactions due to ABO incompatibility are comparable. The reported fatality rate is 5–24%. The most widely cited figure is 5–10% [3]. TRALI is the leading cause of transfusion-related death in the USA [15]. Assuming an incidence of 1 in 5,000, there are many TRALI-associated deaths. In the USA there are approximately 20,000,000 plasma-containing components transfused annually (2005 data). If the death rate is 5–10%, there are 200–400 TRALI deaths per year in the USA.

As reported by Davis et al. [16], milder forms of TRALI exist which do not meet the consensus definition. TRALI reactions are likely to represent a clinical spectrum. Therefore, the true incidence of this syndrome may be significantly higher than what has been reported.

Pathogenesis

As with incidence, the precise mechanism of TRALI is not known. There are two working hypotheses – leukocyte antibodies and the 2-event ('hit') model (the 2-event model is described elsewhere in this issue of the journal and as such will not be covered in this article). Almost certainly, there are other mechanisms at play. It is clear that there is overlap of these mechanisms. Whatever the mechanism, the final pathway involves increased pulmonary microvascular permeability and its attendant pulmonary edema.

The pathology of TRALI is that of the ARDS, in which there is interstitial and alveolar edema and extravasated neutrophils in the alveolar spaces [17, 18]. Capillary leukostasis is a constant feature and its presence correlates with the amount of proteinaceous fluid in the alveoli. In autopsy cases, Dry et al. [19] found a correlation between capillary leukostasis and desquamated epithelial cells. Hyaline membranes and injury to the pulmonary architecture have been reported [17, 19, 20]. The association of leukocyte antibodies with TRALI was initially recognized in the 1970s. Over the last 35 years many investigators have confirmed the presence of HLA class I anti-

bodies and human neutrophil antibodies (HNA) [1, 3, 15, 17, 20]. In the Mayo Clinic series an antibody-containing blood component was found in 89% of cases [3]. In approximately 50% of cases the antibody corresponds to the cognate antigen in the recipient [3]. Many investigators have corroborated these findings [5]. In approximately 5–10% of cases, the antibody is identified in the pre-transfusion serum of the patient [5, 21]. Interdonor TRALI has been reported which involves antibodies in one blood component reacting against antigens in another component being transfused to the same recipient [22]. In 5–15% of cases, no antibody is found in either the patient or donor [21].

Some HLA class I antibodies are known to induce neutrophil aggregation *in vitro*. It is assumed that these antibodies also prime and activate neutrophils and such activation is currently viewed as pivotal in the initiation of TRALI [20]. While most reports link HLA class I antibodies, in recent years class II antibodies have also been implicated. Kopko et al. [23] found such antibodies in two cases and in combination with class I in 5 cases. As HLA class II antigens are not expressed on human neutrophils, it is unclear how such antibodies trigger TRALI. Kopko et al. [23] has suggested binding of HLA class II antibodies to monocytes with subsequent release of cytokines and neutrophil activation as an alternate pathway to induction of the syndrome.

HNA antibodies 1a, 1b and 2a have been reported to be associated with severe forms of TRALI [25–27]. HNA-3a is believed to be particularly potent, with fatal cases following FFP or platelet components published recently [20, 26]. HNA-3a and other neutrophil antibodies has been demonstrated to prime neutrophils *in vitro* [20]. In the isolated *ex vivo* rabbit lung model of Seeger et al. [28], HNA-3a antibodies, HNA-positive neutrophils, and complement resulted in significant lung edema within 3–6 h. The role of complement activation in the induction of TRALI remains unclear.

The role of multiparous donor plasma in the causation of TRALI has been frequently cited. In a prospective, randomized study of patients receiving FFP in the intensive care unit, patients were transfused with FFP from multiparous (3 or more pregnancies) or non-multiparous donors [29]. Four patients in the multiparous arm developed clinical reactions, one of which was TRALI. The PaO₂/FiO₂ ratio was significantly decreased in the multiparous arm, suggesting that such plasma impairs lung function. The mechanism of such effects requires investigation.

Prevention

Because the profile of the at-risk transfusion recipient is unknown, approaches which address our current understanding of TRALI are needed to reduce its incidence. As allogeneic plasma appears to be the constant, strategies which reduce the number of exposures to plasma are appropriate. It is premature to conclude which of these approaches is most effective.

1. Because of the strong association between female plasma and TRALI, the National Blood Service (NBS) of the UK introduced a 'male-only' FFP policy in 2004. Plasma from females was not discarded but it was diverted to fractionation pools for blood derivative manufacture. The impact of this change has had an immediate impact on cases of TRALI reports. As measured by the NBS Serious Hazards of Transfusion Hemovigilance system, the number of incidents and deaths decreased by more than half [30]. The residual cases are associated with whole-blood platelets and RBC. In 2006 blood collectors in the USA began implementing male-only policies, and early data indicate a similar diminution in TRALI cases [31].
2. Prospective screening of plasma from multiparous donors (two or three pregnancies) for HLA (and HNA antibodies): When antibodies are identified, the plasma should be diverted for uses other whole blood, FFP or platelets.
3. Multicomponent collection of blood components using apheresis (MCA): Apheresis technology allows a blood collector to obtain therapeutic doses of high-quality blood components through strong process control [32]. The safety profile of such collections is excellent. The number of adverse events is reported to be the same or less than with manual collection procedures [33]. MCA protocols include i) the collection of single-donor platelets (SDP); ii) 1 SDP and 2 FFP (double unit); iii) 3 FFP (triple unit); iv) 1 RBC and 2 FFP; and v) 2-RBC. If the products collected by MCA are transfused to a single recipient, the risk of TRALI should be reduced by decreasing allogeneic exposures and the TRALI-inducing content. As indicated by the Quebec Hemovigilance data, the risk of TRALI from apheresis products is less than with whole-blood products [6], underscoring the validity of such an approach.

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