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Recipient Clinical Risk Factors Predominate in Possible Transfusion-Related Acute Lung Injury

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Abstract

Background—Possible transfusion-related acute lung injury (pTRALI) cases by definition have a clear temporal relationship to an alternative recipient risk factor for acute respiratory distress syndrome (ARDS). We questioned whether transfusion factors are important for the development of pTRALI.

Study Design and Methods—In this nested case-control study, we prospectively identified 145 consecutive patients with pTRALI and randomly selected 163 transfused controls over a 4-year period at the University of California, San Francisco and the Mayo Clinic, Rochester.

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Results—For pTRALI, we found evidence against transfusion being important: receipt of plasma from female donors (OR 0.82, 95% CI 0.29 – 2.3, p=0.70), total number of units transfused (OR 0.99, 95% CI 0.89 – 1.10, p=0.86), and number of red blood cell and whole blood units transfused (OR 0.78, 95% CI 0.59 –1.03, p=0.079). In contrast, we found that risk for pTRALI was associated with additional recipient factors: chronic alcohol abuse (OR 12.5, 95% CI 2.8 – 55, p<0.001), current smoker (OR 4.2, 95% CI 1.67 – 10.8, p=0.0024), shock before transfusion (OR 4.6, 95% CI 2.0 – 10.7, p<0.001), and positive fluid balance before transfusion (OR 1.32 per liter, 95% CI 1.20 – 1.44, p<0.001).

Conclusion—Recipient risk factors for ARDS rather than transfusion risk factors predominate in pTRALI.

Keywords

transfusion-related acute lung injury; TRALI; possible TRALI; acute lung injury; acute respiratory distress syndrome; ARDS; transfusion reaction; pulmonary edema

INTRODUCTION

Transfusion-related acute lung injury (TRALI) is defined as new acute lung injury (ALI) that developed during or within 6 hours of transfusion with no temporal relationship to an alternative risk factor for ALI.[1, 2] Possible TRALI (pTRALI) is defined as new ALI that developed during or within 6 hours of transfusion *with* a clear temporal relationship to an alternative risk factor for ALI.[2] In the remainder of this study, while retaining the iconic term TRALI, the term ALI that was used during the study is used interchangeably with the term acute respiratory distress syndrome (ARDS). In fact, the updated Berlin definition of ARDS suggests that the term ARDS should include both ALI and ARDS.[3] Growing evidence suggests that the two conditions, TRALI and pTRALI, are quite different. While the incidence of TRALI decreased with male-predominant plasma strategy[4, 5] the incidence of pTRALI did not.[4] Also, the occurrence of TRALI related to the presence of HLA or HNA antibody in the donor while the occurrence of pTRALI did not.[6] In addition, pTRALI had worse clinical outcomes than TRALI, including higher mortality similar to ARDS.[7] Further studies that shed light on the role of transfusion in the pathophysiology of pTRALI are needed.

We conducted a prospective observational study of post-transfusion hypoxemia at two academic medical centers. This study uniquely included electronic surveillance of patients with post-transfusion hypoxemia, and also included a random sample of concurrent control patients who did not develop hypoxemia after transfusion. The study prospectively identified consecutive cases of TRALI, transfusion-associated circulatory overload (TACO), and pTRALI. In nested case-control studies, we described the risk factors for TRALI[4] and TACO.[8] To shed more light on the pathophysiology of pTRALI, this nested case-control study examined the risk factors for pTRALI.

MATERIALS AND METHODS

Study design

Prospective observational surveillance for post-transfusion hypoxemia was conducted between 2006 and 2009 at the University of California, San Francisco (UCSF, San Francisco, CA) and the Mayo Clinic (Rochester, MN) using an electronic surveillance system to screen for post-transfusion hypoxemia in real time,[9] as previously described.[4] After study coordinators screened the electronic alerts, they sent case information electronically to two critical care physicians on the four-member Expert Panel (O.G., R.H., M.R.L., M.A.G.). Each expert independently classified each case as TRALI, pTRALI, TACO, TACO/TRALI, or other. The final diagnosis was that agreed upon independently by two experts. For quality assurance, all TRALI cases that had another ALI risk factor present, and cases in which only one reviewer diagnosed TRALI, were reviewed at conference calls with all four members of the Expert Panel. The case-control design was nested within the prospective case-finding study. Among the cases of post-transfusion hypoxemia we identified, there were 145 cases of pTRALI. We enrolled 163 concurrent control patients who had been transfused but did not experience hypoxemia. The Institutional Review Board at each institution approved the study design. All red blood cell units transfused were prestorage leukocyte reduced.

Definition of TRALI and possible TRALI

TRALI was defined as new ALI that developed during or within 6 hours of transfusion with no temporal relationship to an alternative risk factor for ALI.[1, 2] Possible TRALI was defined as new ALI that developed during or within 6 hours of transfusion where there was a clear temporal relationship to an alternative risk factor for ALI.[2] Major ALI risk factors were sepsis, pneumonia, aspiration, multiple fractures, and pancreatitis. Other ALI risk factors were acute central nervous system injury or stroke, disseminated intravascular coagulation, post-lung resection, lung radiation, near drowning, heat stroke, lung contusion, drug overdose, burn, exposure to high altitude, or receiving amiodarone. Cases designated as pTRALI in this study were patients in whom the Expert Panel thought the new ALI had a clear temporal relationship to the recipient ALI risk factor.

STATISTICAL METHODS

Descriptive data

Descriptive summaries (Table 1) include percentages, mean, standard deviation, median, and range. We do not include p-values because the purpose of the table is descriptive, and the association of the characteristics with pTRALI was more appropriately assessed by the multivariate modeling that accounted for the sampling weights for the controls.

Multivariate models

By definition, all pTRALI cases had one or more ARDS risk factors clearly temporally related to the onset of the new ARDS. To determine whether there were additional pTRALI recipient factors, we tested the recipient risk factors we had found for TRALI.[4] Our reasoning was that since both pTRALI and TRALI are permeability pulmonary edema

conditions, we expected the recipient risk factors to be the same. The six TRALI recipient risk factors we had previously found by multivariate analysis (by examining 130 candidate recipient factors) were chronic alcohol abuse, current smoking, shock, positive fluid balance, peak airway pressure while being mechanically ventilated, and liver surgery.[4] We used these six variables for the pTRALI recipient risk factor multivariate model. We then added three transfusion potential risk factors one at a time to the recipient risk factor multivariate model. Models used the surveylogistic procedure (SAS statistical software, SAS Institute, Cary, NC) to account for the stratified design and oversampling of controls with larger numbers of transfused units. We note that we could not evaluate the ALI risk factors used by the Expert Panel to define pTRALI, because the recipient ALI risk factor was present by definition in every member of the pTRALI group. One cannot test factors that are part of the case definition.

RESULTS

Table 1 describes the pTRALI cases (N=145), and controls (N=163) that did not develop pulmonary edema after transfusion. Of the 145 cases of pTRALI, the major ALI risk factors that had a clear temporal relationship to the onset of ALI included sepsis (n=61), pneumonia (n=20), aspiration (n=15), multiple fractures (n=2) and pancreatitis (n=2). A pTRALI case could have had more than one ALI risk factor.

Transfusion factors

Table 2 shows evidence that transfusion factors were not strongly associated with pTRALI, including whether the patient received any female plasma or whole blood, and the total number of blood components transfused during or within six hours. Since multiple red blood cell units have been associated with ARDS in the past,[10] we tested this possibility also and found no increase in risk with increasing number of red blood cell and whole blood units.

Recipient factors

In pTRALI cases, by definition, one or more recipient ALI risk factors were clearly temporally related to the onset of ALI. In Table 2, we show additional recipient factors that increased the risk of pTRALI, including chronic alcohol abuse, current smoking, shock before transfusion, and larger fluid balance before transfusion.

DISCUSSION

We found that in contrast to TRALI,[4] receipt of plasma from female donor(s) and larger number of transfused units were not risk factors for pTRALI. We also found that additional recipient factors known to increase the risk of ARDS were significantly associated with the development of pTRALI.

We found chronic alcohol abuse, current smoking, shock and positive fluid balance to increase risk for pTRALI. While not included as ALI risk factors described in the Methods section that defined pTRALI, these recipient factors are known to modify and increase risk and manifestations of ARDS patients, transfused or not transfused. Chronic alcohol

abuse,[11,12] smoking,[12,13,14] and shock,[10,15,16] all increase the risk for ARDS. Liberal fluid administration is associated with worse clinical manifestations and outcomes in ARDS.[17]

Fluid overload is classically thought to exist in hydrostatic edema but not permeability edema. Currently, we know that there is overlap, and fluid overload can be observed in a significant proportion of patients with permeability edema. The ARDS Clinical Trials Network clearly showed that almost 1/3 of clinically-defined ARDS cases actually have pulmonary capillary wedge pressure readings that are consistent with hydrostatic edema.[18] We also found positive fluid balance to be associated with increased risk in TACO[8] and TRALI.[4]

The Leukocyte Antibody Prevalence Study-II (LAPS-II) study showed that the occurrence of pTRALI was unrelated to HLA antibody status of the blood product donor and therefore pTRALI was likely not a result of the blood transfusion.[6] This data and our findings in this study explain the observation that TRALI incidence decreased but pTRALI incidence did not decrease with implementation of transfusion of plasma from predominately male donors.[4] This implies different etiologies for TRALI and pTRALI, and suggests that TRALI is related to transfused donor leukocyte antibodies, whereas pTRALI is related mainly to recipient ARDS risk factors.

Our previous finding of different clinical outcomes of TRALI and pTRALI cases lends further support to this idea that the underlying recipient ARDS risk factor(s) are more important than transfusion factors in pTRALI patients. Possible TRALI patients had worse clinical outcomes including a higher mortality (42%) compared to TRALI patients (17%).[7] Indeed, the known mortality of ARDS of 35–40%[10] is nearly identical to the observed 42% mortality of pTRALI,[7] suggesting that ARDS risk factors and not transfusion risk factors are driving the clinical outcomes in pTRALI cases.

TRALI and pTRALI thus appear to have different etiologies, effective mitigation strategies and clinical outcomes. In epidemiological reports, the impulse may be to lump TRALI and pTRALI cases into one category, especially since TRALI is a rare complication that has decreased in incidence with plasma mitigation strategies, but we discourage this practice. To distinguish pTRALI from TRALI, one must identify a risk factor for ARDS (sepsis, pneumonia, aspiration, multiple fractures, pancreatitis and others[1,2]) with a clear temporal relationship to new ARDS that develops during or within 6 hours of transfusion.

In the evaluation of a transfusion reaction case for TRALI, Transfusion Medicine physicians may find it difficult to identify recipient ARDS risk factors, and the list of these factors may change with further research.[16] Speaking with the clinicians, the patient's physician or a critical care consultant would clarify whether the patient has a risk factor for ARDS clearly temporally related to the onset of pulmonary edema. If so, the transfusion reaction report can state that the case is transfused ARDS, and transfusion is unlikely to be an important contributing factor.

In the past, the occurrence of ARDS has been reported to be associated with multiple units of red blood cell transfusion.[10, 19] However, the cases reported were likely a mixture of TRALI and pTRALI cases, and possibly some contribution from TACO cases. The analyses

of red blood cell transfusion as a risk factor did not control for whether or not the recipients received plasma from female donors. If TRALI and TACO cases were removed from transfused ARDS cases, then increasing number of red blood cell units may not be a risk factor for ARDS. Indeed, we found no additional risk of pTRALI with increasing number of units of red blood cells and whole blood transfused (Table 2). Similarly, in our study of TRALI,[4] we initially found that increasing number of transfused units was associated with increased risk. However, when we controlled for receipt of donor leukocyte antibodies, we found that the risk of even 10 or more units became small and was no longer statistically significant at OR of 1.05 (95%CI, 0.91–1.20) per unit more than 9 (p=0.53). The donor antibody variables explained away the risk of increasing number of units transfused.[4] Thus, multiple transfusions in itself appears not to be an independent risk factor for ARDS. We suggest that “multiple transfusions” no longer be considered an independent ARDS risk factor, as the cause of ARDS in these cases appears to be receipt of antibody-containing donor plasma.

Our study was limited by our inability to test all recipient leukocyte HLA antigens, and to test for leukocyte HLA and HNA antibody in the plasma of all donors of units transfused to the pTRALI cases. Thus, we could not determine whether larger amounts of matching strong anti-HLA-class II and anti-HNA in donor units might be risk factors as in TRALI.[4] However, donor leukocyte antibodies are unlikely risk factors for pTRALI, as we found female plasma was not a strong risk factor (Table 2). Also, we could not formally evaluate the underlying ARDS major risk factors (including sepsis, pneumonia, aspiration, multiple fractures and pancreatitis) clearly temporally related to the new onset of ALI, because factors in the pTRALI case definition cannot be evaluated as risk factors. Since those ARDS risk factors are well-established and clearly temporally related to the new ALI, it is likely that they played the major role in the development of ALI in the pTRALI cases, and that the additional recipient factors that we found increased the risk further. We examined only recipient risk factors important for TRALI, and there may be additional recipient risk factors. However, our conclusion that recipient factors predominate in pTRALI does not change, if there are additional pTRALI recipient risk factors we did not examine. In addition, we did not specifically test for phospholipids in the plasma of leukocyte reduced red blood cell units because this possibility was not published before the onset of our study.[19] However, this is unlikely, because we found the number of leukocyte reduced red blood cell units and whole blood transfused was not a strong risk factor (Table 2). The small number of patients with liver surgery or peak airway pressure greater than 30 mm H_20 rendered the OR estimates imprecise with wide 95% CI. Also of note is that the upper bounds of the confidence limits for transfusion factors exceeded 1.0 (Table 2), and it is possible that in some of the pTRALI cases, donor antibodies played some role.

In conclusion, we found evidence against transfusion being important for pTRALI, suggesting that the primary cause was the recipient ARDS risk factor with a clear temporal relationship to the onset of new lung injury, and other additional recipient risk factors known to increase the risk of ARDS. It is well-known that ARDS can occur in patients who are not transfused. Thus, pTRALI is likely a misnomer, and “transfused ARDS” may be a more appropriate designation for cases of ARDS during or after transfusion, where recipient ARDS risk factors predominate.

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Abbreviations

Anti-HLA-Class II	antibody to Class II human leukocyte antigen
Anti-HNA	antibody to human neutrophil antigen
ALI	acute lung injury
ARDS	acute respiratory distress syndrome
HLA	human leukocyte antigen
HNA	human neutrophil antigen
TRALI	transfusion related acute lung injury
pTRALI	possible TRALI, ALI/ARDS within six hours after transfusion, with a clear temporal relationship to an alternative recipient risk factor for ALI/ARDS
TACO	transfusion-associated circulatory overload and hydrostatic pulmonary edema

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Table 1

Description of control and pTRALI groups.

	Controls (N=163)	**pTRALI (N=145)**
Age		
Age in years, mean ± SD (N)	56 ± 20 (N=163)	58 ± 19 (N=145)
Age in years, median (min-max)	59 (1–98)	61 (94–97)
Gender		
Female	73 (45%)	70 (48%)
Male	90 (55%)	75 (52%)
Total	163	145
TRANSFUSION FACTORS:		
Receipt of plasma or whole blood from female donor(s)		
No	109 (67%)	99 (68%)
Yes	54 (33%)	46 (32%)
Total	163	145
RBC or whole blood units, mean ± SD (N)	2.6± 2.4 (N=163)	2.3± 3.3 (N=145)
RBC or whole blood units, median (min-max)	2 (0–12)	1 (0–17)
Units (any component) received within 6 hours, mean ± SD, (N)	6.0 ± 5.2 (N=163)	5.0 ± 5.6 (N=145)
Units (any component) received within 6 hours, median (min-max)	3 (1–21)	3 (1–35)
RECIPIENT FACTORS in addition to those clearly temporally related to the new ALI:		
Chronic alcohol abuse		
No	154 (97%)	118 (85%)
Yes	5 (3%)	21 (15%)
Total	163	139
Current smoker		
No	144 (89%)	109 (78%)
Yes	18 (11%)	30 (22%)
Total	162	139
Shock before transfusion		
No	133 (82%)	80 (55%)
Yes	30 (18%)	65 (45%)
Total	163	145
Fluid balance before transfusion in liters, mean ± SD (N)	2.7 ± 3.3 (N=155)	5.2 ± 5.3 (N=142)
Fluid balance before transfusion in liters, median (min-max)	2 (−5 to 16.1)	4.4 (−1.8 to 44.5)
Peak airway pressure >30 cm H_20 within 12 hours of intubation before transfusion		
No	156 (96%)	131 (90%)
Yes	7 (4%)	14 (10%)
Total	163	145
Liver surgery (transplantation)		

	Controls (N=163)	**pTRALI (N=145)**
No	158 (97%)	143 (99%)
Yes	5 (3%)	2 (1%)
Total	163	145

Note: We do not include p-values because the purpose of the table is descriptive, not univariate analyses. The association of the characteristics with pTRALI was more appropriately assessed by the multivariate modeling that accounted for the sampling weights for the controls in Table 2.

Table 2

Multivariate model of recipient and transfusion risk factors for pTRALI by survey logistics analysis.

	Odds ratio	Lower 95%CI	Upper 95%CI	p-value
Candidate recipient factors, in addition to the ALI risk factor(s)clearly temporally related to the onset of ALI:				
Chronic alcohol abuse	12.5	2.8	55	<0.001
Current smoker vs. never or former smoker	4.2	1.67	10.8	0.0024
Shock before transfusion	4.6	2.0	10.7	<0.001
Fluid balance before transfusion, increment per liter	1.32	1.20	1.44	<0.001
Peak airway pressure >30 cm H_20 within 12 hours after intubation &before transfusion	0.47	0.08	2.7	0.39
Liver surgery (transplantation)	0.77	0.08	7.7	0.82
Results of single additions of transfusion factors to the above multivariate model:				
Receipt of plasma or whole blood from female donor(s)	0.82	0.29	2.3	0.70
Number of units (any component) transfused during or within 6 hours of ALI	0.99	0.89	1.10	0.86
Number of red blood cell and whole blood units transfused during or within 6 hours of ALI	0.78	0.59	1.03	0.079