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Transfusion related acute lung injury after transfusion of maternal blood: a case control study

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Abstract

Study Design—This is a single center retrospective case control study of 7 Transfusion Related Acute Lung Injury (TRALI) cases and 28 controls in the pediatric spinal surgery population.

Objective—To determine the association between maternal transfusion and risk of TRALI in pediatric spinal surgery patients.

Summary of Background Data—Previous studies support a “two-hit” model for the pathogenesis of TRALI – activation and sequestration of neutrophils in the pulmonary vasculature followed by transfusion of a biologic response modifier such as anti-leukocyte antibodies. Maternal donation of blood products is a potential risk factor for TRALI due to the development of anti-leukocyte antibodies during pregnancy. Until now there have been no studies specifically addressing the risk of TRALI following maternal transfusions.

Methods—This is a retrospective case control study of 7 TRALI cases with 4 controls per case, matched by strata for volume of plasma transfused. All cases identified by the Transfusion Biology and Medicine Specialized Center of Clinically Oriented Research (SCCOR) with a TRALI diagnosis were eligible for inclusion. Electronic medical records and operative notes were reviewed to obtain demographic data, diagnosis, surgical approach and number of spine levels for each operation.

Results—An increased prevalence of maternal blood transfusion was found among the TRALI cases compared to the control cases: 43% (3 of 7) versus 7% (2 of 28), $p = 0.044$. There were otherwise no statistical differences between the groups, including age, gender, surgical approach, number of spinal levels, or type of blood product transfused.

Conclusions—Pediatric patients undergoing spinal surgery may be at increased risk for the development of TRALI following the transfusion of maternal blood products. Accordingly, we recommend that directed donation of maternal blood products should be avoided in this population. This study also found that TRALI may be under-recognized and under-reported to the transfusion service.

INTRODUCTION

Transfusion Related Acute Lung Injury (TRALI) is currently the leading cause of transfusion related fatalities.¹ TRALI is defined as the new onset of acute lung injury (ALI) occurring within 6 hours of blood product transfusion.² Radiologic findings in TRALI demonstrate

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This study was approved by the institutional review board at the University of California San Francisco.

bilateral pulmonary infiltrates occurring in the absence of fluid overload and/or cardiac failure.² Early studies examining the pathogenesis of TRALI hypothesized that lung injury was caused by an immune reaction based on the observation that many of the implicated blood products contained granulocyte or lymphocytotoxic antibodies, the majority of which had human leukocyte antigen (HLA) specificity.³ This hypothesis is supported by data demonstrating that 83% of TRALI fatalities are associated with anti-leukocyte antibodies.⁴ However, the antibody theory does not explain those TRALI cases which occur in the absence of demonstrable anti-leukocyte antibodies and to account for these cases a “two-hit” model for the pathogenesis of TRALI has been proposed.⁵ In this model, the first hit is the activation and sequestration of neutrophils in the pulmonary vasculature caused by a predisposing clinical condition, such as surgery or infection.⁶ The second hit, which results in TRALI, occurs through the transfusion of biologic response modifiers, either anti-leukocyte antibodies with recipient antigen specificity or bioactive lipids accumulated during blood product storage.⁷ This model is supported by recent animal studies which suggest that inflammation increases susceptibility for TRALI by sequestration of neutrophils in the lung.⁸

There are multiple case reports of TRALI occurring in the pediatric population and many of these have been associated with the presence of donor anti-leukocyte antibodies which are incompatible with the blood product recipient.^{9–18} Several of these case reports have involved children who received maternal blood product transfusions.^{16–18} Maternal directed donations are potentially problematic since pregnancy is a known risk factor for the development of antibodies against paternal antigens and the prevalence of anti-HLA antibodies has been shown to increase with each subsequent pregnancy.¹⁹ Interventions to mitigate the risk of TRALI have focused on minimizing the preparation of high plasma volume components from donors implicated in previous TRALI reactions and those thought to be at high risk of having anti-leukocyte antibodies.²⁰ These guidelines have not specifically addressed the issue of maternal directed donations even though the theoretical risk associated with maternal blood product transfusion has long been recognized.^{10, 21}

Patients undergoing spinal surgery frequently demonstrate evidence of acute lung injury²² and may be at increased risk for TRALI.²³ There is a single previous case report which describes TRALI occurring in a pediatric spinal surgery patient receiving a maternal blood product transfusion.¹⁷ In this particular case, the donated blood product from the patient’s mother was found to contain an HLA antibody with specificity for paternal HLA antigens present in the patient.¹⁷

Our institution, in collaboration with the Mayo Clinic, is currently conducting a five year prospective study to determine the incidence of TRALI and identify recipient and donor risk factors. As part of this study, potential TRALI cases are identified using continuous electronic surveillance to detect all patients developing new hypoxemia within twelve hours of any blood product issued from the blood bank. All confirmed TRALI cases require consensus diagnosis from two independent critical care experts following the National Heart, Lung, and Blood Institute working group definition of TRALI.² Diagnostic criteria includes the acute onset of hypoxemia defined as a PaO₂/FiO₂ ratio of less than or equal to 300 mmHg, radiographic evidence of bilateral pulmonary edema occurring in the absence of left atrial hypertension and blood product transfusion occurring within the preceding 6 hours. The four critical care experts responsible for reviewing potential TRALI cases that are detected via electronic surveillance include recognized experts in the field of critical care medicine who are well versed at distinguishing pulmonary edema caused by vascular permeability (TRALI) from hydrostatic pulmonary edema due to fluid overload.²⁴ As part of the larger prospective TRALI study, this panel has reviewed greater than 700 cases of pulmonary edema following blood product transfusion. At our institution, this panel identified three TRALI cases in pediatric patients

undergoing spinal surgery who received maternal blood product transfusions between March 2006 and February 2009.

CASE 1

An 11-year-old girl with Trisomy 18, spastic quadriplegia and progressive scoliosis underwent corrective posterior spinal fusion from T1-L4. Intraoperatively she received a red blood cell unit and a fresh frozen plasma (FFP) unit from her brother. Later in the case she became tachycardic and subsequently received one unit of red blood cells from her mother resulting in a decrease in oxygen saturation to 94% on a fractional inspired O₂ concentration (FiO₂) of 0.56 with a partial pressure of oxygen in arterial blood (PaO₂) to FiO₂ ratio of 211. Upon arrival to the Intensive Care Unit (ICU) a chest radiograph showed development of severe pulmonary edema. A review of the complete blood counts revealed that after transfusion of the maternal red blood cells the white blood cell count dropped precipitously from $14.3 \times 10^9 \text{ L}^{-1}$ to $2.6 \times 10^9/\text{L}$. Ten hours after the surgery, the white blood cell count returned to $8.2 \times 10^9/\text{L}$. This reaction was reported to the hospital transfusion service as a possible transfusion reaction. The transfusion reaction work-up including a hemolysis check and DAT or Coomb's test was negative indicating that there was no evidence of a hemolytic transfusion reaction. This type of transfusion reaction, however, is not typically associated with lung injury. Additional testing was then performed to evaluate for antibody mediated TRALI. Of the three blood products the patient received, the maternal red cell unit had antibodies that matched four of the patient's HLA Class II antigens, DQ7, DR12, DR4 and DR52. Neither the FFP nor the red blood cell unit donated by her brother had HLA antibodies. She was extubated 18 hours after surgery.

CASE 2

A 16-year-old girl with scoliosis underwent posterior spinal fusion. During surgery she received six blood products including one maternally donated whole blood unit. At the conclusion of the procedure she was extubated, however, one hour later her PaO₂ dropped to the 70s and she was re-intubated. At this time a respiratory exam revealed coarse rales and pink frothy fluid discharged from the endotracheal tube. A chest radiograph revealed moderate diffuse pulmonary edema. The patient's urine output increased after administration of furosemide, but no change was seen on repeat chest radiograph an hour later. The maternally donated whole blood unit was found to have multiple antibodies that matched the patient's HLA Class I antigens A2 and B58, as well as the patient's HLA Class II antigens DR13 and DR52. The mother also had an anti-neutrophil antibody. The grandmother who donated one unit of whole blood also had HLA antibodies, but none matched the patient's antigens. A sister who donated one unit of whole blood had an anti-neutrophil antibody but no HLA antibodies. The remaining three blood products were donated by three unrelated volunteer male donors, none of whom had antibodies to HLA or human neutrophil antigens.

CASE 3

A 9-year-old girl with early onset idiopathic scoliosis underwent anterior spinal fusion from T10 to L3. During the procedure she received two units of whole blood. She was extubated in the operating room and received two more whole blood units in the Post-Anesthesia Care Unit (PACU). However, she developed low oxygen saturation and required increased FiO₂. A dose of furosemide was given, and a chest radiograph was obtained which revealed bilateral lower lobe atelectasis and bilateral pleural effusions. She was transferred to the ICU where her oxygen saturation dropped briefly to 70 necessitating high-flow oxygen and biphasic positive airways pressure (BiPAP) until post-operative day two. The transfused blood products were two whole blood units from her mother and one whole blood unit from her father. Blood from her mother tested positive for multiple HLA antibodies directed against the HLA antigens DR4, DR16, DQ7, DQ8 and DQ9. The mother refused HLA antigen typing of the patient.

Based on these three cases and our current understanding of the pathogenesis of TRALI, maternal directed donations for pediatric spinal surgery cases are no longer permitted at our institution as a precautionary measure for patient safety. To determine further evidence to support this change in policy, a case-control study was designed to determine whether there is an association between maternal blood product transfusion and the development of TRALI.

MATERIALS AND METHODS

This study was approved by the institutional review board at the University of California San Francisco. The Transfusion Biology and Medicine Specialized Center of Clinically Oriented Research (SCCOR) study is currently examining the incidence and major risk factors for TRALI. As part of this study, all patients hospitalized at the University of California San Francisco are continuously monitored via electronic surveillance to detect potential TRALI cases.²⁵ Those patients who develop hypoxemia within 12 hours of blood product issue as defined by a PaO₂/FiO₂ ratio of less than 300 mmHg or an operating room hemoglobin oxygen saturation of less than 97% are independently evaluated by two critical care experts for TRALI diagnosis. All cases receiving a TRALI diagnosis as part of the SCCOR study were eligible for inclusion in this case control study.

A review of SCCOR data from March 2006 through February 2009 identified a total of seven TRALI cases in the pediatric spinal surgery population, three of whom received maternal transfusion and are described above. Using these seven cases, a retrospective case control study was designed to determine whether maternal transfusion is associated with an increased risk of TRALI. Patients eligible for study inclusion were all pediatric patients less than or equal to 18 years of age undergoing anterior and/or posterior fusion spinal surgery (International Classification of Diseases-9 codes 81.04, 81.05, 81.06 and 81.08) requiring peri-operative or intra-operative blood product transfusion from March 2006 through February 2009. For all eligible patients, blood bank records were reviewed to determine the number and type of blood products transfused. Due to the substantial variation in both number and type of blood products transfused, cases and potential controls were stratified based on the volume of plasma transfused into a moderate plasma volume group (280–2000 ml, or the equivalent of more than one but less than nine high volume plasma units such as FFP, platelets or whole blood) and a high plasma volume group (>2000 mL). In order to estimate the volume of plasma transfused, high volume plasma products such as FFP, platelets and whole blood were estimated to contain 250 mL of plasma, while red cells were estimated to contain 30 ml and cryoprecipitate 20 mL. Four controls per case, matched by strata for volume of plasma transfused, were selected using a random sequence generator.

Electronic medical records were then reviewed to obtain demographic data including age, sex, diagnosis and procedure codes for all cases and controls. Additionally, operative notes were reviewed to determine the surgical approach and number of spine levels for each operation. Finally, donor records were reviewed to identify all patients who received maternal donations. Fisher's exact test was used to examine the association between categorical variables and TRALI based on the two-tailed P value.

RESULTS

Demographic and clinical categorical data are summarized in Table 1. The only statistically significant difference between cases and controls was an increased prevalence of maternal blood transfusion among the TRALI cases. The cases also demonstrated a trend towards being more likely to have received any directed donor blood but this was not statistically significant and likely reflects that those patients who received maternal blood are also more likely to receive directed donations from other family members. The majority of TRALI cases were

female, although this difference was not statistically significant. There was a trend towards younger patients within the TRALI group but this was also not statistically significant. Most of the TRALI cases received a moderate number of units transfused. Although whole blood transfusion has been shown to be associated with an increased risk of TRALI in a previous study²³, we saw no statistically significant difference in whole blood transfusion between the cases and controls. There were also no statistically significant differences between cases and controls in terms of the other types of components transfused including red blood cells, platelets and FFP. TRALI occurred in patients undergoing anterior or posterior spinal surgery and did not appear to be associated with the number of spinal levels.

DISCUSSION

This case control study is the first to describe and association between the transfusion of maternal blood products and TRALI in pediatric patients undergoing anterior and/or posterior spinal surgery. This association had been previously suspected based on multiple case reports of patients developing TRALI after receiving maternal blood product transfusion in a variety of clinical settings including spinal surgery.^{16–18}

Based on our current understanding of TRALI mechanisms, the transfusion of virtually any blood product containing anti-HLA or human neutrophil antibodies corresponding to cognate antigens present in the blood product recipient could predispose the recipient toward the development of TRALI. Pregnancy is a known risk factor for the development of anti-HLA antibodies.¹⁹ These antibodies are directed against paternal antigens present in the fetus which the mother lacks and recognizes as foreign. Once formed these antibodies may persist for many years after the pregnancy. In this study, cases 1 and 2 both developed TRALI following maternal blood product transfusion and laboratory testing identified multiple anti-HLA antibodies present in the mother which were concordant with HLA antigens present in the child. Anti-neutrophil antibodies are also implicated in the pathogenesis of TRALI and case two demonstrated the presence of this type of antibody in the mother in addition to concordant anti-HLA antibodies. Case three also demonstrated the presence of anti-HLA antibodies in the mother, however, further testing to determine the HLA type of the child was not permitted so concordance could not be established. However, since the mother in this case had no history of blood transfusion, pregnancy would have been the stimulus for these antibodies and there is a high likelihood that concordance would have been demonstrated had testing been permitted.

While other family members who provide directed donation, particularly female relatives with a history of prior pregnancy, can also possess anti-HLA or anti-neutrophil antibodies, it is less likely that these antibodies will be concordant with the child recipient. Of the three cases in this study who developed TRALI following maternal transfusion, only case 2 received directed donations from other female relatives. Laboratory testing demonstrated anti-HLA antibodies in a grandmother who had a history of four pregnancies but these were not concordant with recipient antigens. An anti-neutrophil antibody of uncertain clinical significance was detected in a sister who had no prior pregnancy history.

Although the estimated incidence of TRALI is 1:5000 transfusions³, the true incidence remains unknown because prior estimates have been based on only those cases reported to the blood bank which may underestimate the incidence if cases are unrecognized or unreported. Of the seven TRALI cases occurring in pediatric spinal surgery patients in this study, only one was reported to the hospital blood bank. This suggests that true incidence of TRALI may be much higher, not just in the pediatric spinal surgery population but in all hospital populations.

It is still incompletely understood why some patients who receive cognate antibodies through transfusion develop TRALI while others do not. Current research indicates that neutrophil

priming appears to play a role, possibly predisposing a patient for the development of TRALI should transfusion of cognate antibodies occur.⁶ A previous case control study suggested spinal surgery may be a risk factor for TRALI.²³ This observation would be biologically plausible given our current understanding of TRALI as neutrophil priming would occur from the inflammation caused by the nature and duration of spinal surgery. At our institution we observed seven TRALI cases over three years among 55 pediatric spinal surgery patients requiring 389 blood product transfusions. Based on current TRALI estimates, this suggests an increased risk of TRALI in the pediatric spinal surgery population. All TRALI cases in this study were identified as part of a large prospective study to determine the incidence of TRALI and recipient risk factors. Although results from the larger study are not yet published, it is interesting to note that the three pediatric spinal surgery patients highlighted in this study that developed TRALI and received maternal blood transfusions were the only cases of maternal transfusion associated TRALI observed in the larger study.

Although donors with a history of pregnancy are likely to have formed anti-leukocyte antibodies directed against paternal antigens present in the fetus, it is not currently the standard of care to routinely test blood donors for these antibodies. However, in an effort to reduce TRALI risk, national blood bank guidelines were established in the fall of 2006 to minimize the preparation of high plasma volume components from patients at risk of leukocyte alloimmunization. Based on these guidelines, our donor center implemented a policy in the fall of 2007 prohibiting the preparation of plasma or whole blood components from women with a history of pregnancy. Cases 2 and 3 which were both due to maternal whole blood transfusion occurred prior to this change in policy and would have been prevented under the new guidelines. In spite of these efforts, case 1 occurred after the change in policy as the implicated product was a red blood cell unit. TRALI can occur following the transfusion of red blood cells and has been attributed to the small amount of residual plasma.²⁶

Maternal directed donations are no longer permitted for pediatric patients undergoing spinal surgery at our institution. This policy change occurred following the observation of three TRALI cases in our pediatric spinal surgery population and one prior case reported in the literature. Our current understanding of the pathogenesis of TRALI supports this change in practice as multiparous women are known to be high risk for the development of anti-HLA or anti-neutrophil antibodies and these antibodies likely correspond to antigens present in the child. These antibodies can be present in all blood components including low plasma volume components such as red blood cells.²⁶

Pediatric patients undergoing spinal surgery may be at increased risk for the development of TRALI following the transfusion of cognate antibodies, possibly due to an increased risk of neutrophil priming associated with the surgical procedure or the patient's underlying disease. This case control study demonstrates that there is an association between maternal transfusion and the development of TRALI in the pediatric spinal surgery population.

This study is a single institution retrospective case control study focused only on pediatric patients undergoing spinal surgery. These findings may not necessarily be extrapolated to other institutions or other surgical populations. The primary limitation of this study is the small sample size. During the study period, fewer than 60 pediatric spinal surgeries requiring blood product transfusion were performed at our institution. This small sample size prevented additional case-control matching strategies to eliminate potential confounders such as age. Multivariate statistical analysis to control for such potential confounders would only be possible in the setting of a much larger study. Our study is also limited by the small number of TRALI cases. This is due in part to the infrequency of TRALI and in part to a change in practice prohibiting maternal blood product donation for pediatric spinal surgery after several cases were observed. Our institution continues to allow maternal donation for other types of

pediatric surgeries and this practice is most frequently used for cardiac surgery. These patients differ from the pediatric spinal surgery population in that they are typically infants who are transfused washed red blood cells. The washing process is used to prevent transfusion of potassium which accumulates during red cell storage but also removes plasma and any maternal antibodies the plasma may contain. Future studies should examine the association between maternal transfusion and TRALI in other pediatric populations utilizing maternal transfusion.

This study demonstrates an association between the transfusion of maternal blood products and the development of TRALI in pediatric patients undergoing anterior and/or posterior spinal surgery. TRALI appears to occur frequently in this population and may be under-recognized and under-reported to the transfusion service. In an effort to minimize the risk of TRALI, directed donation of blood products from mother to child should be avoided in this patient population.

Key Points

1. Transfusion of maternal blood products is associated with an increased risk of TRALI in pediatric patients undergoing anterior and/or posterior spinal surgery.
2. To minimize risk of TRALI, directed donation of blood products from mother to child should be avoided in this patient population.
3. TRALI may be under-recognized and under-reported to the transfusion service.

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Table 1

Demographic and Clinical Data*

	Cases (n = 7)	Controls (n = 28)	P value
Gender			0.20
Male	1 (14)	14 (50)	
Female	6 (86)	14 (50)	
Age			0.075
6 to 12 years	5 (71)	8 (29)	
13 to 18 years	2 (29)	20 (71)	
Number of Units Transfused			0.67
Moderate (2–8)	5 (71)	15 (54)	
High (9+)	2 (29)	13 (46)	
Type of Blood Product Transfused			
Any Red Blood Cells	5 (71)	26 (93)	0.45
Any Fresh Frozen Plasma	6 (86)	25 (89)	1.00
Any Platelets	2 (29)	8 (29)	1.00
Any Whole Blood	3 (43)	7 (25)	0.38
Any Directed Donor	3 (43)	5 (18)	0.31
Product[†]			
Any Maternal Blood	3 (43)	2 (7)	0.044
Surgical Approach[‡]			
Anterior	3 (43)	7 (25)	0.38
Posterior	6 (86)	28 (100)	0.20
Number of Anterior Spine Levels			1.00
Anterior < 7	2 (67)	4 (57)	
Anterior 7+	1 (33)	3 (43)	
Number of Posterior Spine Levels			0.31
Posterior <13	3 (50)	6 (21)	
Posterior 13+	3 (50)	22 (79)	

* Data displayed as number (percentage).

[†] Includes maternal donations

[‡] Two cases and seven controls had combined anterior and posterior surgeries and one case had anterior surgery only.