Transfusion.
TRALI and TACO OB

Jose M. Rivers, MD*

*Associate Professor. Baylor College of Medicine. Houston, Texas

CAUSES OF MATERNAL DEATH

- Severe bleeding (Haemorrhage) 25%
- Infection 15%
- Eclampsia 12%
- Obstructed labour 7%
- Unsafe abortion 13%
- Other direct causes 8%
- Indirect causes 20%


TRANSFUSION REQUIREMENTS IN CRITICAL CARE (TRICC)

Prospective, randomized trial that supports causal link between blood transfusion and adverse outcomes among critically ill patients


TRANSFUSION FACTS

- 80 million units donated worldwide yearly
- 20 million units transfused each year in the United States
- A blood transfusion is the most intimate possible contact with a stranger

BLOOD TRANSFUSION COMPLICATIONS

Relationship between the number of units of blood and postoperative complications. Columns indicate the percentage of complications related to the number of units of blood transfer

BLOOD TRANSFUSION COMPLICATIONS

- Infectious disease
- Complications resulting from misidentification or clerical error
- Transfusion-related acute lung injury
- Bacterial contamination
- Immunomodulation
- Unknown mechanism

NONINFECTIOUS SERIOUS HAZARDS OF TRANSFUSION (NISHOTS)\(^a\)

Immune mediated
- Hemolytic transfusion reaction
- Febrile nonhemolytic transfusion reactions
- Allergic/urticarial/anaphylactic transfusion reaction
- Transfusion-related acute lung injury (TRALI)
- Posttransfusion purpura (PTP)
- Transfusion-associated graft versus host disease (TA-GVHD)
- Microchimerism
- Transfusion-related immunomodulation (TRIM)
- Alloimmunization

Nonimmune mediated
- Septic transfusion reactions
- Nonimmune hemolysis
- Mistransfusion
- Transfusion-associated circulatory overload (TACO)
- Metabolic derangements
- Coagulopathic complications from massive transfusion
- Complications from red cell storage lesions
- Over/Undertransfusion
- Iron overload

INFECTIOUS DISEASES

- Human immunodeficiency virus risk: 1:2.3 million\(^1\)
- Hepatitis C risk: 1:1.8 million\(^1\)
- Hepatitis B: 78,000 new infections annually, United States\(^2\)
- Risk of transmission through transfusion of 1 unit of blood, 1:58,000-1:149,000\(^3\)
- Other viral diseases\(^4,5\)
- West Nile: 2539-9862 cases in United States between 2002 and 2006\(^4\)
- Cytomegalovirus: 40%-100% of US population shows prior exposure by serology\(^5\)
- Malaria: 300-500 million cases worldwide\(^6\)
- Chagas disease: »1 million new cases annually\(^6\)
- Prions\(^6\)

*In humans, confined to South and Central America and Mexico.

Relationship between the number of units of blood and mortality columns indicate the percentage of non-survivors in relation to the number of units of blood transfused
PATIENT IDENTIFICATION IS CRITICAL

- Identify at time of phlebotomy
- Ask patient his/her name
- Verify identity with wrist band
- Label tube at bedside
- Identify at time of transfusion
  - Two people must identify patient and verify match to label on blood product
- If there are ANY discrepancies when blood sample and paperwork arrive at blood bank
  - It is 40 times more likely that the wrong patient’s blood is in the tube than if all identifying information is complete and matches

WHAT IS TRALI AND TACO

- TRALI
  - Transfusion-related acute lung injury
- TACO
  - Transfusion associated circulatory overload
  - Pulmonary complications of blood transfusions

SUMMARY OF TRANSFUSION ERRORS 2006-2009

- Medication administered with blood
- Patient refused but transfused
- Transfused but not indicated
- Contra-indicated medication
- Computer related error
- Technical error
- Wrong ABO FFP transfused
- No crossmatch but transfused
- Mislabeled crossmatch sample
- Units transfused/not ordered
- Misidentified on issue/transfusion

DATA ON FILE, US DEPARTMENT OF VETERANS AFFAIRS.

TRANSFUSION-RELATED FATALITIES BY COMPLICATIONS, FY 2005 THROUGH FY 2008

<table>
<thead>
<tr>
<th>Year</th>
<th>TRALI</th>
<th>HTR (non-ABO)</th>
<th>Microbial infection</th>
<th>HTR (ABO)</th>
<th>TACO</th>
<th>Anaphylaxis</th>
<th>Other</th>
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</thead>
<tbody>
<tr>
<td>FY 05</td>
<td>29</td>
<td>16</td>
<td>8</td>
<td>6</td>
<td>1</td>
<td>0</td>
<td>2</td>
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<tr>
<td>FY 06</td>
<td>35</td>
<td>9</td>
<td>7</td>
<td>3</td>
<td>8</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>FY 07</td>
<td>34</td>
<td>2</td>
<td>6</td>
<td>3</td>
<td>5</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>FY 08</td>
<td>16</td>
<td>7</td>
<td>7</td>
<td>10</td>
<td>3</td>
<td>3</td>
<td>0</td>
</tr>
</tbody>
</table>
Case Report

Transfusion-related acute lung injury (TRALI) in an obstetric patient

L. Michala*, B. Madhavan, N. Win, C. De Lord, R. Brown

Princess Royal University Hospital, Farnborough Common, Orpington, UK. The National Blood Service, Tooting Centre, London, UK and the Department of Obstetrics and Gynaecology, McGill University, Montreal, Canada

SUMMARY: Transfusion-related acute lung injury (TRALI) is the leading cause of mortality following transfusion of blood products. Despite increasing awareness, the condition often remains unrecognized and therefore underreported. A 28-year-old with moderate pre-eclampsia had a post-partum haemorrhage following emergency caesarean section. Shortly after receiving three units of packed red cells she went into respiratory failure, which progressed to cardiac arrest. She was successfully resuscitated and made a slow but full recovery. Investigation through the National Blood Service confirmed the diagnosis of TRALI. TRALI is an increasingly common life-threatening complication of blood transfusion and should be included in the differential diagnosis of collapse in an obstetric patient who has recently received a blood product transfusion.

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Introduction

Transfusion-related acute lung injury (TRALI) is a form of adult respiratory distress syndrome (ARDS) that occurs following transfusion of blood products. TRALI was first described as an entity in 1985, but it is only in the last five years that it has gained recognition as a leading cause of morbidity and mortality following transfusion. Haemorrhage and blood transfusion are common events in the obstetric setting. Nevertheless few cases of TRALI have been reported in obstetric patients, suggesting that the condition may often remain undetected.

Case History

A 28-year-old African primigravida, with no past medical history of note, presented with pre-eclampsia at 40 weeks of gestation. Her condition was deemed stable and at first she did not require antihypertensive treatment. She went into spontaneous labour at 40 weeks and 4 days. She received epidural analgesia and, despite oxytocic augmentation, required caesarean delivery for failure to progress. Surgery was performed under epidural anaesthesia. A live male infant was delivered in good condition. During labour, fluid intake was restricted to 85 mL/h. The urine output was monitored closely and was maintained at an average of 30 mL/h. The estimated blood loss at caesarean section was 1000 mL. She remained haemodynamically stable throughout the procedure and received 1000 mL of Hartmann’s solution. Platelet count, and renal and liver function at the onset of labour and 2 h post partum were within normal limits. She remained hypertensive after delivery and was started on labetalol 200 mg three times daily. Thromboprophylaxis in the form of enoxaparin 40 mg was administered daily after delivery.

On the third postoperative day the woman was noted to have a haemoglobin concentration of 6.7 g/dL, and was transfused three units of cross-matched red cells in additive

* Correspondence to: Lina Michala, UCL Institute of Women’s Health, Eliza Garrett Anderson and Obstetric Hospital, Huntley Street, London WCIE 6DH. E-mail: lina.michala@uclh.nhs.uk.
Case report

Severe transfusion-related acute lung injury managed with extracorporeal membrane oxygenation (ECMO) in an obstetric patient

Allison J. Lee MD (Assistant Professor of Clinical Anesthesiology)\textsuperscript{a,*},
Pushpa L. Koyyalamudi MD (Anesthesiologist)\textsuperscript{b},
Ricardo Martínez-Ruiz MD (Assistant Professor of Clinical Anesthesiology)\textsuperscript{a}

\textsuperscript{a}Department of Anesthesiology, Perioperative Medicine, and Pain Management, University of Miami Leonard L. Miller School of Medicine, Miami, FL, USA
\textsuperscript{b}Anesthesiology Associates, Hudson, FL, USA

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Anesthesia;
Obstetric;
Extracorporeal membrane oxygenation;
Transfusion-related acute lung injury

Abstract. Transfusion-related acute lung injury (TRALI) is the leading cause of transfusion-related mortality in the United States. Management is usually supportive, including supplemental oxygen, intravenous fluids, and mechanical ventilation if necessary. Most patients recover within 72 hours. We present a nearly fatal case of TRALI in an obstetric patient, which was successfully managed with extracorporeal membrane oxygenation (ECMO).

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1. Introduction

Transfusion-related acute lung injury (TRALI), defined by the NIH working group, is new acute lung injury (ALI) occurring during or within 6 hours of a transfusion [1,2]. Acute lung injury is acute hypoxemia with an arterial oxygen concentration/fraction of inspired oxygen (P\textsubscript{a}O\textsubscript{2}/\text{FiO}\textsubscript{2}) ratio ≤300 mmHg or oxygen saturation ≤90% when a patient is breathing room air, found together with the appearance of bilateral infiltrates in the absence of left atrial hypertension [1,2].

All plasma-containing blood products have been implicated in TRALI, including packed red blood cells (PRBCs), whole blood, intravenous (IV) gamma globulin, and cryoprecipitate but, most commonly, whole blood-derived platelet concentrates and fresh frozen plasma (FFP) [3]. Most patients recover within 72 hours and treatment is supportive, rarely requiring more than mechanical ventilation [3].

We present a case of severe TRALI, which was nearly fatal in an obstetric patient, but was successfully managed with extracorporeal membrane oxygenation (ECMO).

2. Case report

A 22-year-old, gravida 3, para 2 woman presented at 40 weeks' gestation with mild vaginal bleeding. She had a history of one prior classical cesarean delivery and she was to undergo an urgent repeat cesarean delivery. Combined
CASE PRESENTATION

- 22 year-old, ASA I G3P2 at 40 weeks with vaginal bleeding.
- One prior classical cesarean delivery
- She was to undergo urgent repeat C/S
- CSE was performed without complications with hyperbaric bupivacaine 0.75% (10 mg), fentanyl 10 μg and 0.2 mg preservative-free morphine
- After delivery severe uterine atony.
- Pitocin 30 units by continuous infusion
- Methylergonovine 0.2 mg IM
- Carboprost X 2 IM and intramyometrial
- Hemodynamically stable for first 45 minutes
- Hypotension and significant oozing in surgical field.
- Supracervical hysterectomy
- EBL: 4 L. LR: 6 L. Hetastarch: 500 cc
- PRBCs 7 units. FFP 6 units Platelets: 10 units
- During skin closure: Dyspnea, tachypnea and O₂ saturation 85%
- Mental changes
- RSI, intubation and mechanical ventilation
- Copious amount of frothy secretions
- Transferred to SICU
- PA catheter placed: PCWP: 16 mmHG, PA pressure 46/30, CO 6.0 L/min
- Over next 2 hours worsening hypotension and hypoxemia
- Norepinephrine infusion and vasopressin
- Increasing ventilatory support
- Inhaled nitric oxide.
- Nine hours postoperatively. Veno-Arterial ECMO.
- Soon after ECMO, patient hemodynamically stable. Mechanical ventilation weaned over next seven days
- Discharged home on postoperative day 33

DIFFERENTIAL DIAGNOSIS OF TRANSFUSION ASSOCIATED-RESPIRATORY DISTRESS

- TRALI
- Circulatory Overload (TACO)
- Allergic/Anaphylactic transfusion reaction
- Bacterial contamination
- Acute hemolytic reaction
- Not transfusion related

TRANSFUSION-RELATED ACUTE LUNG INJURY (TRALI)

- First cases described in 1950’s
- AKA
  - Pulmonary leukoaglutinin reaction
  - Allergic pulmonary edema
  - Pulmonary hypersensitivity reaction
  - Non-cardiogenic pulmonary edema
- TRALI coined by Popovsky and Moore

TRALI

- Defined as ALI/ARDS developing during or within 6 hours of a blood product transfusion
- Immunologic reaction leading directly to ALI
- Must exclude volume overload or cardiogenic pulmonary edema
- Must exclude other causes of ALI/ARDS
2004 CONSENSUS PANEL CRITERIA FOR TRALI

- Acute lung injury
- Acute onset
- Hypoxemia
  - $\text{SPO}_{2} < 90\%$ on room air or other clinical evidence of hypoxemia
  - $\text{PaO}_{2}/\text{FiO}_{2}$ ratio $< 300$ mmHg
  - Bilateral infiltrates on frontal CXR
  - No evidence of left atrial hypertension (e.g. circulatory overload)
  - No preexisting ALI before transfusion
  - During or within 6 hours of transfusion
  - No temporal relationship to an alternative risk factor for ALI

Transfusion 2004;44:1774-1789

TRALI-Epidemiology

- Incidence:
  - 1-5,000 blood products transfused
  - 1 in 400 patients transfused
  - Under-reported and under-recognized
  - Fatal in 5-10% cases

Differential Diagnosis of Transfusion Associated-Respiratory Distress

PATHOGENESIS

- TRALI has been associated with all plasma-containing products
  - Whole blood, PRBCs, FFP, platelets are the most commonly identified causes.
  - Allogenic stem cells, cryoprecipitate, intravenous immunoglobulin and granulocytes
  - High plasma volume products (FFP and platelets) are the most implicated products
  - Even small amounts of plasma can trigger the reaction.
THREE HYPOTHESIS FOR TRALI

- Antibodies to human leukocyte antigens or antigranulocyte antibodies in donor’s plasma (or, less commonly, recipient’s plasma)
- Biologically active substances in transfused blood
- “2-hit” hypothesis
  - Recipient granulocytes are primed in vivo, then transfused antibodies «activate» granulocytes


PATHOGENESIS

Effect of blood product storage time

- Corpuscular and supernatant effects
- RBCs become more rigid
- Cytokines accumulate with increased storage time; pro-inflammatory lipids accumulate
  - Less of a problem with universal leukoreduction

THREE HYPOTHESIS FOR TRALI

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TRALI: 2-HIT HYPOTHESIS

Predisposing condition

- Recent surgery
- Trauma
- Active infection or inflammation
- Cytokine administration
- Massive transfusion

Blood products (any)

- Anti-granulocyte antibodies
- Anti-HLA antibodies
- Biologically active lipids
TRALI: PATHOGENESIS

Pulmonary edema

Increased microvascular permeability

Leukocyte antibodies

2«event» model

TRALI: WHO IS AT RISK?

• Recent surgery
• Induction chemotherapy
• Cardiopulmonary bypass
• Massive transfusion
• TTP
• No difference in gender, age


CLINICAL FEATURES

• Onset
  • Sudden
• Classically, 30-60 min after initiation of transfusion, with a range of 0-6 hours
• Signs and symptoms
  • Fever, hypotension, tachycardia, and tachypnea
  • Hypoxemia often requiring mechanical ventilation
  • CXR: bilateral alveolar infiltrates consistent with ALI/ARDS

TREATMENT

• Stop the transfusion!
• Rule out other causes of pulmonary edema, especially volume overload or cardiac dysfunction
• Possibility of co-existing permeability and hydrostatic edema
• ARDSnet ventilatory strategy
• Diuretics may be harmful
• No role for corticosteroids
• Remember that with supportive care, most patients will recover quickly
Screening of multiparous women to avoid transfusion-related acute lung injury: a single centre experience

U. J. H. Sachs, E. Link, C. Hofmann, W. Wasel & G. Bein Institute for Clinical Immunology and Transfusion Medicine, Justus Liebig University, Giessen, Germany
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SUMMARY. The aim of this study was to investigate which approach for serological testing of multiparous donors might be feasible and effective to reduce the risk of transfusion-related acute lung injury (TRALI). TRALI is a serious adverse event of blood transfusion. Antibodies to granulocytes and human leucocyte antigens (HLAs) are frequently detected in sera of implicated donors. These donors are often multiparous women. A general deferral of female plasma or screening strategies for leucocyte antibodies has been proposed to increase blood safety. A prospective study was initiated in 2003. Until 2006, serum samples from all female donors reporting three or more pregnancies (n = 229) were screened for the presence of antibodies against granulocytes and HLAs by immunofluorescence and agglutination tests as well as by a commercial HLA enzyme immunoassay. In total, 40% of all multiparous women were reactive in one of the assays. Twenty-nine percent of the reactive sera contained antibodies to granulocytes but not to HLAs. During the observation period, three TRALI reactions occurred in our hospital, two of which would have been prevented if the screening program had been extended to all previously pregnant donors. We conclude from these data that, not unexpectedly, the number of previous pregnancies is not a reliable indicator for the likelihood of inducing TRALI. More importantly, screening strategies for antibodies that might induce TRALI should probably not be reduced to HLA antibody screening. This finding awaits further research.

Key words: granulocyte serology, HLA antibodies, TRALI.

Transfusion-related acute lung injury (TRALI) is a serious, life-threatening syndrome that presents as acute hypoxaemia and non-cardiogenic pulmonary oedema during or within 6 h after blood transfusion. In the recent years, TRALI has been shown to be the most common cause of transfusion-related fatalities in the United States and the UK (Stainsby et al., 2003; Holmes et al., 2004). The exact pathogenesis of TRALI has not yet been elucidated, but the activation of neutrophils has been identified as being pivotal in TRALI (Silliman et al., 2005; Bux & Sachs, 2007). An interplay between endogenous triggers (e.g. trauma or sepsis) and exogenous substances has been postulated to precipitate this activation, either in two steps (two-step model) (Silliman, 2006) or in multiple steps that are necessary to overcome an interindividually different activation threshold (threshold model) (Bux & Sachs, 2007). Exogenous substances that have been identified in blood products that caused clinical TRALI include lipids, which may accumulate in cellular blood components during storage, and leucocyte antibodies, which are present in the plasma of immunized donors. When Popovsky and Moore (1985) first identified TRALI as a distinct clinical entity, they reported granulocyte-reactive antibodies in the sera of 89% of blood donors implicated in 36 cases of TRALI. Subsequently, antibodies to both, granulocytes and human leucocyte antigens (HLAs), were found by many other investigators in sera of implicated blood donors (Yomtovian et al., 1984; Nordhagen et al., 1986; Eastlund et al., 1989; Bux et al., 1996; Santamaria et al., 1995; Leger et al., 1999; Kopko et al., 2001; Davoren et al., 2003). The donor of such antibody-containing blood components is often a
**TRALI OUTCOMES**

<table>
<thead>
<tr>
<th>Condition</th>
<th>Cases (n)</th>
<th>Cases (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oxygen support</td>
<td>36</td>
<td>100</td>
</tr>
<tr>
<td>Mechanical ventilation</td>
<td>26</td>
<td>72</td>
</tr>
<tr>
<td>Pulmonary infiltrates</td>
<td>36</td>
<td>100</td>
</tr>
<tr>
<td>Rapid resolution (&lt; 96 h)</td>
<td>29</td>
<td>81</td>
</tr>
<tr>
<td>Slow resolution (&gt; 7 days)</td>
<td>6</td>
<td>17</td>
</tr>
<tr>
<td>Mortality</td>
<td>2</td>
<td>6</td>
</tr>
<tr>
<td>Long-term sequelae</td>
<td>0</td>
<td></td>
</tr>
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</table>

**TRALI PREVENTION**

- Mutiparous donors
  - 20-25% possess HLA antibodies
  - Implicated in look-back studies (Kopko, JAMA)
  - 1/3 of female apheresis donors in one study
- UK SHOT initiative
  - Male only FFP
  - Pooled platelets suspended in male plasma
- AABB has recommended that high plasma volume blood products (FFP), platelets be obtained from males or females with no history of pregnancy
  - Female donors>>>PRBCs and other plasma-poor products
  - FFP policy has been implemented
  - Platelet deferral ongoing

**CONCLUSION**

- TRALI is the #1 cause of transfusion-associated mortality
- TRALI is a clinical diagnosis that can be made at the bedside
- Blood within 6 hours + ALI/ARDS = TRALI
- Role of HLA and neutrophil antibodies and prevention in TRALI

**TRANSFUSION-ASSOCIATED CIRCULATORY OVERLOAD (TACO)**

**Definition/mechanism**

- Pulmonary edema due to transfusion
- Too much blood + non-sanguineous fluid
- Transfused too rapidly
- Cardiogenic
- Role of cytokines?

**TACO: CLINICAL PROFILE**

- Risk factors: Very young/old
- Onset: < 2 hours of transfusion
- Symptoms: Respiratory distress, cyanosis, headache, dry cough
- Signs: ↑BP; systolic > diastolic; ↑HR;
  - ↑CVP: ↑ wedge pressure
- Laboratory: ↑ B-natriuretic peptide

**TACO: MANAGEMENT**

- Stop transfusion
- Provide supplementary oxygen
- Reduce plasma volume with diuretics
- Place patient in sitting position
- If symptoms continue:
  - Repeat the use of diuretics
  - Phlebotomize in 250 mL increments
- Laboratory testing:
  - First tier testing
TACO: SUMMARY

- TACO is an important clinical diagnosis
- Significant morbidity
- Increased recognition of mortality
- It is a frequent complication of transfusion
- It is under-recognized and under-diagnosed
- Confused with TRALI

TRALI vs TACO

Comparison of the features of transfusion related acute lung injury and transfusion associated circulatory overload

<table>
<thead>
<tr>
<th>Feature</th>
<th>TRALI</th>
<th>TACO</th>
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</thead>
<tbody>
<tr>
<td>Body temperature</td>
<td>Fever can be present</td>
<td>Unchanged</td>
</tr>
<tr>
<td>Blood pressure</td>
<td>Hypotension</td>
<td>Hypertension</td>
</tr>
<tr>
<td>Respiratory symptoms</td>
<td>Acute dyspnea</td>
<td>Acute dyspnea</td>
</tr>
<tr>
<td>Neck veins</td>
<td>Unchanged</td>
<td>Can be distended</td>
</tr>
<tr>
<td>Auscultation</td>
<td>Rales</td>
<td>Rales, S3 may be present</td>
</tr>
<tr>
<td>Chest radiograph</td>
<td>Diffuse, bilateral infiltrates</td>
<td>Diffuse, bilateral infiltrates</td>
</tr>
<tr>
<td>PA occlusion pressure</td>
<td>18 mmHg or less</td>
<td>Greater than 18 mmHg</td>
</tr>
<tr>
<td>Pulmonary edema fluid</td>
<td>Exudate</td>
<td>Transudate</td>
</tr>
<tr>
<td>Fluid balance</td>
<td>Positive, even, negative</td>
<td>Positive</td>
</tr>
<tr>
<td>Response to diuretic</td>
<td>Minimal</td>
<td>Significant</td>
</tr>
<tr>
<td>White count</td>
<td>Transient leukopenia</td>
<td>Unchanged</td>
</tr>
<tr>
<td>BNP</td>
<td>&lt; 200 pg/mL</td>
<td>&gt;1,200 pg/mL</td>
</tr>
<tr>
<td>Leukocyte antibodies</td>
<td>Donor leukocyte antibodies present, crossmatch incompatibility between donor and recipient</td>
<td>Donor leukocyte antibodies may or may not be present, positive results can suggest TRALI even with true TACO cases</td>
</tr>
</tbody>
</table>

Transfusion-related fatalities by complications, FY 2005 through FY 2008