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IDENTIFYING TRANSFUSION-RELATED ACUTE LUNG INJURY IN THE ANESTHETIZED PATIENT

by

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Bachelor of Science in Nursing, University of North Dakota, 2001

An Independent Study

Submitted to the Graduate Faculty

of the

University of North Dakota

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for the degree of

Master of Science

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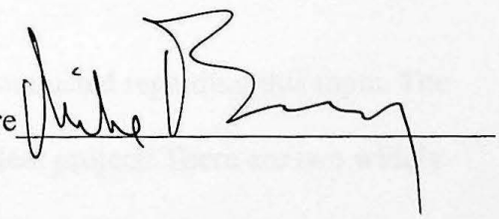
Signature 

Date 10-23-12

Abstract

Blood transfusions are an important part therapy for patients undergoing surgical procedures. Blood transfusions often begin in the operating room (OR) while under the care of the Certified Registered Nurse Anesthetist (CRNA) or Student Registered Nurse Anesthetist (SRNA). Transfusions have many therapeutic and life-saving benefits for patients, however transfusion of blood products also present risks for patients. Transfusion related acute lung injury (TRALI) is a type of non-hemolytic transfusion reaction (NHTR) that occurs when antibodies or other biological modifiers are inadvertently transfused with blood product to a recipient causing endothelial damage to the pulmonary vasculature resulting in leaky epithelium causing pulmonary edema resulting in hypoxemia. The reported incidence rate of TRALI is 0.02% per unit transfused but because it is often under-recognized and underreported true incidence is unknown (Shander & Popovsky, 2005).

Transfusion-associated circulatory overload (TACO) has many of the same presenting characteristics as TRALI and it is thought that patients that may be diagnosed as having TRALI may be incorrectly diagnosed as TACO. Incorrect diagnosis leads to incorrect treatment and therefore could lead to compromising patient outcome.

An extensive evidence based literature review was conducted regarding this topic. The physiological framework was utilized to guide this independent project. There are two widely accepted theories that exist regarding the cause of TRALI following blood transfusion. These include an immune mediated (antibody) mechanism and a non-immune "two-hit" mechanism. This information, when provided to SRNAs and CRNAs, will raise awareness of the complications associated with blood transfusions as well as help with identification and differentiation of TRALI from TACO.

Introduction

Non-hemolytic transfusion reactions (NHTR's) are the most common transfusion reactions and include transfusion-related acute lung injury (TRALI), allergic reactions, febrile reactions, hypotension, bacterial sepsis, transfusion-associated circulatory overload (TACO), and metabolic complications. TRALI is one of the most serious forms of NHTR's with mortality rates around 0.2% (Hirayama, 2010).

TRALI is often misdiagnosed and often confused with transfusion-associated circulatory overload (TACO). The misdiagnoses of TRALI often delays and/or completely leads to incorrect treatment of TRALI which could compromise patients respiratory and cardiovascular systems and overall health. It is important for anesthesia providers to be aware of the signs and symptoms of TRALI as well as the treatment to optimize patient overall well-being.

Purpose

The purpose of this project is to identify and understand why transfusion related acute lung injury (TRALI) is under-recognized and why it is often mistaken for transfusion-associated circulatory overload (TACO). This project will discuss the pathophysiology of both TRALI and TACO and how each clinically presents to the anesthesia provider.

The goal is to identify compounding factors such as patient health history, intravascular fluid volume status, serum brain natriuretic peptide status, pulmonary edema protein presence and how each relates to both TRALI and TACO. These factors will assist anesthesia providers for proper identification of TRALI and TACO and allow for accurate treatment and better prognosis for patients.

Significance

TRALI has been associated with a variety of blood products including whole blood, packed red blood cells, fresh frozen plasma, granulocytes, cryoprecipitate, platelet concentrates, apheresis platelets, allogeneic bone marrow, intravenous immunoglobulin, and peripheral blood progenitor cells (Roberts, 2004). Although TRALI has been associated with all components of blood, blood components that contain greater than 50 mL of plasma are most implicated. Plasma rich components that have the highest association with the development of TRALI include FFP and apheresis platelets. True incidence of TRALI is unknown due to its relatively recent developed standardized definition. Initially, incidence of 1:5000 per unit of blood component transfused with more recent reports ranging to 1:432 for whole blood platelets to 1:557,000 for red blood cells (Triulzi, 2009). The reported mortality rate of TRALI is 5-10% with a reported mortality rate of 8% in critically ill patients in the intensive care units making these patients the most susceptible to developing TRALI (Silliman, Fung, Ball, & Khan, 2009).

Theoretical Framework

Development of TRALI in patients is not fully understood and there is no clear pathogenesis of TRALI. There have been multiple mechanisms studied with two mechanisms receiving most support. These include an immune (antibody)-mediated mechanism as well as a non-immune "two-hit" mechanism.

The first and oldest mechanism of TRALI suggests that it is an alloimmunization reaction in which alloantibodies are activated against HLA's or human leukocyte antigens (Class 1 and 2) found on leukocytes. The antigen-antibody reaction results in activation of granulocytes which adhere to the pulmonary endothelium, causing damage to the endothelium resulting in permeability and leading to pulmonary edema. HLA antibodies (Class 1 and 2) are thought to

develop in woman as a response to pregnancy and in individuals that have received previous blood transfusions (Joyce, 2007).

HLA antibodies are found to be highest in multiparous females. In 2003, the United Kingdom began a TRALI risk reduction strategy by supplying fresh-frozen plasma (FFP) from predominantly male donors, which resulted in a large decrease in reported TRALI cases. A surveillance study from 2003 to 2005 reported to the American Red Cross indicated that 71% of 38 reported probable TRALI deaths and 75% (18/24) deaths from transfused plasma were from WBC antibody-positive female donors. This prompted the American Association of Blood Banks (AABB) to publish an Association Bulletin in November 2006 to reduce the risk of TRALI. The bulletin recommended using blood products only when necessary, minimizing the preparation of high plasma volume components (FFP or apheresis platelets) from known leukocyte alloimmunized donors or those at increased risk of alloimmunization (Triulzi et al, 2009).

The Leukocyte Antibody Prevalence Study (LAPS) was designed to measure the prevalence of HLA antibody's in donors with or without a history of pregnancy or blood transfusions. The LAPS was conducted between December 2006 and May 2007 as a prospective cross-sectional multicenter study by the National Heart, lung, and Blood Institute's (NHLBI). The 8171 blood donors enrolled (6011 female, 2160 male) gave consent to give a blood sample and complete short questionnaire regarding history of pregnancy and past blood transfusions. Of the 8171 enrollees, 7920 (96.9%) had valid HLA antibody test results. The prevalence of Class I and/or Class II HLA antibody for males receiving transfusion was 1.7% and 1.0% non-transfused. The prevalence for Class I and/or Class II HLA antibody for females overall was 1006/5834 (17.2%). The prevalence for Class I and/or Class II HLA antibody with previous pregnancy reported 973/3992 (24.4%). Of the 1006 females tested positive for Class I or II HLA

antibody, 973 reported previous pregnancies (96.7%) indicating a high association between previous pregnancy and HLA alloimmunization. Also noted was an increase in HLA antibody in woman with greater numbers of pregnancies: 1.7% (zero pregnancy), 11.2% (one), 22.3% (two), 27.5% (three), and 32.2% (four or more pregnancies). These results show strong support for the development of HLA antibodies in multiparous females as well as the immune (antibody)-mediated mechanism for the development of TRALI. (Triulzi et al, 2009).

Although there has been strong experimental and clinical evidence to support the immune mediated mechanism of TRALI, there have been approximately 15% of cases in which antibodies have not been found in cases of TRALI. A "two-hit" model has been proposed by Sillimen et al (1997) to explain this mechanism of TRALI. The "first-hit" would be an initial stressor that the patient would experience such as severe infection, surgery, trauma, or massive transfusion which causes an initial insult to vascular endothelium. This causes endothelial activation, release of cytokines, and expression of adhesion molecules. The cytokines than attract and prime neutrophils, which adhere to the endothelium. The "second-hit" activates sequestered neutrophils to release oxidases and proteases, causing damage to the endothelium, which leads to capillary leak and acute lung injury. The proposed cause for the "second-hit" may be facilitated by the transfusion of biological modifiers such as leukocyte antibodies, lipid priming molecules, cytokines, or endotoxins (Triulzi, 2006).

Research has shown that when blood component is stored, lipids that rapidly prime neutrophil (PMN) oxidase develop. Silliman et al (1997) did a study to determine the association of biologically active lipids in stored blood and the development of TRALI in patients with an underlying factor of infection, cytokine administration, recent surgery, or massive transfusion.

The study included ten patients with suspected TRALI and ten patients that had either

febrile reactions or urticarial reactions (control group) following transfusion of plasma containing blood products. Twenty-three donors provided blood products for the study, nine males and fourteen females. Sixteen of the 23 donors agreed to participate in the study. Of the eleven females who participated, six were multiparous (defined as ≥ 3 pregnancies), two were primiparous, three had never been pregnant and none of donors had received a blood transfusion. Of the seven donors who didn't participate in the study, three were female with unknown history of pregnancy and four were male with unknown history of blood transfusion. All sixteen donors were tested for the presence of HLA antibodies with six showing weak positivity, with no anti HLA-DR reactions seen, two were male, and one female with no history of ever being pregnant. The two male and one female with no history of pregnancy had no history of receiving a blood transfusion. This shows that of the ten patients with suspected TRALI, about 50% did not receive blood from donors with detectable HLA antibodies (Silliman et al, 1997).

All ten suspected TRALI patients had one of more clinical conditions of active infection and inflammation, recent surgery, cytokine administration and massive transfusion (≥ one blood volume/day for four days). The suspected TRALI patients showed signs and symptoms of TRALI (acute onset hypoxemia), six of the ten patients had chest x-rays that showed bilateral, diffuse fluffy infiltrates, and all ten showed no evidence of cardiac dysfunction. The control group had either febrile reactions (increase in temperature ≥ 1°C with or without chills) or urticarial reactions (acute appearance of hives) during transfusion. The PMN-priming activity was tested pre-transfusion and post-transfusion in all patients. Serum samples of the patients suspected with TRALI were also tested for the presence of HLA and granulocyte antibodies. There were no differences found between the PMN-priming activity of the pre-transfusion and post-transfusion serum samples of the control group. The control group was treated with

acetaminophen and /or diphenhydramine with a quick resolution of symptoms. However, the post-transfusion serum showed a 2.1 fold increase in PMN-priming activity in the suspected TRALI patients, which gives evidence that the lipid priming that occurs during storage of blood product, can play a role in the development of TRALI. Also important to note that in the patients suspected of TRALI there were no HLA antibodies present in post-transfusion serum (Silliman et al, 1997).

Definitions

Acute Lung Injury (ALI): acute onset of bilateral pulmonary infiltrates with hypoxemia without evidence of hydrostatic pulmonary edema caused by injury to both capillary endothelium and alveolar epithelium (Johnson & Matthay, 2010).

Transfusion-Related Acute Lung Injury (TRALI): new acute lung injury (ALI) that develops during or within six hours of receiving any blood product transfusion with no signs of circulatory overload (Looney, Gillis, & Matthay, 2010).

Alloimmunization: an immune response that generates antibodies by one individual in response to antigens from another individual from the same species (O'Toole, 1997).

Nonhemolytic Transfusion Reactions: a type of reaction in which recipient's become sensitized to donor white cells, platelets, or plasma proteins (Morgan, Mikhail, & Murray, 2006).

Multiparous: a woman who has had two or more pregnancies resulting in viable offspring (O'Toole, 1997).

Process

The search of literature for this topic was conducted in an ongoing process from October 2011 – June of 2012 online through the Harley French Library located at the University of North Dakota. A comprehensive review of literature was conducted with the assistance of search engines such as Google Scholar, PubMed and the Cumulative Index to Nursing and Allied Health (CINAHL). The predominance of literature was found within the Harley E. French Medical Library, Cochrane Libraries and Ovid link. Key words that were used to conduct this search were transfusion-related acute lung injury, TRALI, transfusion-associated circulatory overload, TACO, blood transfusion complications, blood transfusion reactions, and anesthesia. The review articles consisted of clinical studies, chart reviews and retrospective reviews. Articles found in American Association of Nurse Anesthesia (AANA) Journal, Transfusion, Chest, Blood Review, Current Opinion in Hematology, Anesthesia & Analgesia and the American Red Cross website, www.redcrossblood.org were reviewed to provide supplemental documentation.

This information was intended to provide education on the pathogenesis of transfusion-related acute lung injury (TRALI), signs and symptoms and transfusion-associated circulatory overload (TACO). This literature review will provide CRNA's and SRNA's with valuable information on how to recognize and differentiate transfusion-related acute lung injury (TRALI) and transfusion-associated circulatory overload (TACO) and the appropriate treatment to provide safe, effective outcomes for the patients they are caring for.

The project was presented to the anesthesia staff of Altru hospital in Grand Forks, ND in June of 2012 and will be presented to the North Dakota Association of Nurse Anesthetists bi-annual meeting in Bismarck, North Dakota in October of 2012.

This project was analyzed and evaluated by an expert reviewer Darla Adams, CRNA, PhD, director of the Nurse Anesthesia Graduate Program at the College of Nursing, University of North Dakota.

Review of Literature

Introduction

The purpose of this section is to examine current evidence-based literature regarding transfusion-related acute lung injury and why it is often misdiagnosed and incorrectly treated because of its similarities to transfusion-associated circulatory overload. Often blood transfusions are started in the operating room under the care of anesthesia providers. TRALI and TACO are two types of non-hemolytic transfusion reactions (NHTR's) that can look very similar in their presentation (acute hypoxia secondary to pulmonary edema) however the pathophysiology is very different. Since there is no single test or clinical feature that distinguishes TRALI and TACO, diagnosis has been made by examining past medical history, pre- and post-lab results, pre- and post-radiological studies and clinical presentation. It is important for the student registered nurse anesthetist and certified registered nurse anesthetist to understand the pathophysiology and diagnostic criteria for TRALI and TACO to help differentiate the two so that early appropriate treatment can be made.

General Information Regarding Blood Transfusions

Blood transfusions are an important part of therapy in health care. Approximately 16 million blood donations are collected each year from approximately 9.5 million donors. Less than 38% of the U.S. population is eligible to donate blood due to medical conditions, recent surgeries, medications, foreign travel, etc. Blood component donations are received by approximately 5 million patients annually (American Red Cross, 2006).

There are four types of transfusable products that can be obtained from blood donation: red blood cells, platelets, plasma and cryoprecipitate. Donors can donate whole blood or specific components only. The process of donating specific components of red blood cells, plasma, or platelets is called apheresis. Apheresis donation results in a much larger amount of individual blood product than can be obtained from a single unit of whole blood. For instance, one unit of platelets can be obtained from a donation of apheresis or by combining the platelets received from five whole blood donations (American Red Cross, 2006)

Non-hemolytic transfusion reactions (NHTR's) are the most common transfusion reactions and include allergic reactions, febrile reactions, hypotension, bacterial sepsis, metabolic complications, transfusion-associated circulatory overload (TACO), and transfusion-related acute lung injury (TRALI). TRALI is one of the most serious forms of NHTR's with mortality rates between 5-10%. (Hirayama, 2010).

Pathogenesis of TACO and TRALI

It is important for the SRNA and CRNA to understand the pathogenesis of TACO and TRALI and differentiate the two so that appropriate treatment can take place. The pathogenesis of TACO is similar to other causes of congestive heart failure. It is caused by an increase in intravascular volume and pulmonary blood volume which leads to an increase in hydrostatic pressure in the pulmonary tissue causing fluid extravasation into the alveolar space causing pulmonary edema and hypoxia.

The incidence of TACO varies from <1% to 8% depending on patient population and reporting method. The highest at risk are the very young (< 3 years of age) the elderly and those with compromised cardiac function (Skeate & Eastlund, 2007). Li et al, (2011) did a two-year prospective cohort study of 901 ICU patients receiving transfusion. They identified 51 patients

(6%) who developed TACO following transfusion. The median age of patients developing TACO was 73 years, 24 were woman and 27 were men. TACO cases received a higher number of transfused units, had larger volume plasma transfused, a more positive fluid balance, and had a faster rate of transfusion. Also noted was those patients that had documented left ventricular dysfunction by echocardiogram prior to transfusion and those receiving FFP for reversal of anticoagulation had a higher incidence of TACO. These results show strong support that patients that are elderly, receive larger volumes, have a more positive fluid balance, receive transfusions at a faster rate, and those with cardiac dysfunction are at greater risk for the development of TACO (Li et al., 2011).

Narick, Triulzi and Yazer, (2012) did a two part study in which the first part was a retrospective analysis of blood bank records from 2003 to 2010 and the second part in which they performed an active surveillance of plasma recipients. They found that 24 patients had a TACO reaction. Fourteen of the 24 patients were ICU patients, 13/24 had comorbidities such as renal failure, congestive heart failure or respiratory failure. Of the 24 patients there were infusion rates were documented for 21 of the patients who experienced TACO. One recipient who had a TACO reaction had a transfusion rate <250 mL/hr., eight patients had transfusion rate between 250-600 mL/hr., and twelve had a transfusion rate >600 mL/hr. The patients received one to ten units of plasma. This study supports the findings that increased infusion rates and comorbidities such as renal failure, congestive heart failure, or respiratory coincide with incidence of TACO (Narick, Triulzi, & Yazer, 2012).

While TACO occurs due to the overwhelmed cardiovascular system by large volume or excessive infusion rate of blood products resulting in pulmonary edema, TRALI, is caused by damage to the pulmonary endothelium which increases permeability. Two mechanisms have

received the most support for the development of TRALI which include and immune-mediated response to human leukocyte antigen (HLA) antibodies as well as a non-immune "two-hit" mechanism. A TRALI incidence of 1:5000 per unit of blood component transfused has been reported with more recent reports ranging from 1:432 for whole blood platelets to 1:557,000 for red blood cells (Triulzi, 2009). The reported mortality rate of TRALI is 5-10% with a reported mortality rate of 8% in critically ill patients in the intensive care units making these patients the most susceptible to developing and dying from TRALI (Silliman, Fung, Ball, & Khan, 2009).

Human leukocyte antigen (HLA) antibodies develop in response to pregnancy or in individuals that have received previous blood transfusions. HLA antibodies are found to be responsible in 60-85% of cases of TRALI. The HLA antibodies are transferred from the donor to the recipient in all blood products. However, blood products with 50 mL of plasma or more are implicated in most cases of TRALI. The transfused HLA antibodies results in an antigen-antibody reaction that activates granulocytes, which adhere to the pulmonary endothelium, causing damage and increasing permeability, resulting in pulmonary edema (Joyce, 2007).

The second mechanism responsible in 15% of TRALI cases is a "Two-hit" mechanism in which a patient experiences an initial event that causes increased stress to a patient such as severe infection, surgery, trauma, or massive transfusion. The first event causes the initial insult to vascular endothelium, causing endothelial activation, release of cytokines, and expression of adhesion molecules. The cytokines than attract and prime neutrophils, which adhere to the endothelium. The "second-hit" activates sequestered neutrophils to release oxidases and proteases, causing damage to the endothelium, which leads to capillary leak and acute lung injury. The proposed cause for the "second-hit" may be facilitated by the transfusion of

biological modifiers such as leukocyte antibodies, lipid priming molecules, cytokines, or endotoxins (Triulzi, 2006).

Diagnostic Criteria

TACO has been recognized for decades, however, there is no universally agreed upon definition of what constitutes TACO. True incidence of TACO is estimated at one in 3000 transfusions to 8% of all transfusions depending upon patient population and reporting methods used (Skeate & Eastlund, 2007).

It has been observed that during or within several hours following transfusion, patients develop respiratory distress. Patients may have orthopnea, cyanosis, tachycardia, hypertension accompanying respiratory distress and rales with an S3 which may be present on auscultation. Patients may have jugular venous distention and lower extremity edema as well. Chest radiograph may reveal cardiomegaly and infiltrates in one or both lungs (Skeate & Eastlund, 2007).

TRALI, or transfusion-related acute lung injury is defined as new acute lung injury (ALI) that develops within six hours from the start of a transfusion of any blood component. Its presentation can be very mild to fulminant, with severe ALI occurring within minutes of the start of a transfusion leading to death in 5-10% of cases, making it one of the leading causes of death related to transfusions (Looney, Gilliss, & Matthay, 2010). Patients develop respiratory distress, hypoxemia, rales on auscultation, and diffuse bilateral infiltrates on chest x-ray with no signs of circulatory overload. Patients may need mechanical ventilation to support oxygenation. Patients may also present with hypotension, fever, and transient leukopenia (Skeate & Eastlund, 2007). The American-European Consensus Conference criteria defines acute lung injury (ALI) as acute onset, with a pulmonary wedge pressure $\leq$ 18 mm Hg when measured, lack of clinical evidence

of left atrial hypertension (CHF), bilateral infiltrates seen on frontal chest radiograph, and hypoxemia demonstrated by a ratio of PaO2/FIO2 $\leq$ 300 regardless of PEEP level (Note: In absence of arterial blood gas, an oxygen saturation of <90% on room air meets criteria for hypoxemia) (Toy & Lowell, 2007).

Distinguishing TRALI from TACO

TRALI can be very difficult to distinguish from other NHTR's especially transfusion associated circulatory overload (TACO). TRALI and TACO have very similar signs and symptoms, there are no diagnostic tests that reliably discriminate the two and the fact that the patient can experience both simultaneously makes it difficult to distinguish TRALI from TACO (Skeate & Eastlund, 2007). Both result in pulmonary edema and hypoxemia within six hours of transfusion, however the distinction of hydrostatic edema is the result of cardiogenic or transfusion associated circulatory overload (TACO) and permeability edema is most often due to non-cardiogenic or acute lung injury (TRALI) (Gajic, Gropper, & Hubmayr, 2006).

Factors that can help distinguish TACO from TRALI include evaluating patient's fluid balance, cardiac function, pulmonary edema fluid, and leukocyte antibody testing. In patients with excess fluid intake pre-transfusion or significant diuresis postreaction, one should consider fluid overload and possibility of TACO (Skeate & Eastlund, 2007).

Cardiac function evaluation can help with determining whether hypoxemic event during or following transfusion is TACO or TRALI. Patients with known congestive heart failure (CHF) or systolic dysfunction on echocardiography may be suggestive of TACO in a post-transfusion reaction (Skeate & Eastlund, 2007).

Pulmonary artery occlusion pressure (PAOP) may help distinguish TACO from TRALI in the presence of pulmonary edema. A PAOP pressure >18 mmHg suggests a cardiogenic cause

to pulmonary edema or TACO and a PAOP pressure <18 mmHG suggests a non-cardiogenic cause or TRALI. However, patients with ALI have been noted to have PAOP >18 mmHG which limits the usefulness of PAOP values in distinction between TRALI and TACO (Skeate & Eastlund, 2007).

Brain natriuretic peptide (BNP) is produced primarily in the cardiac ventricles in response to increased ventricular filling pressure and myocardial stretch. Cardiac monocytes produce pro-brain natriuretic peptide (proBNP). Cardiac stretch causes the release of proBNP from the cardiac monocytes, which is then cleaved to equal portions of BNP and NT-proBNP. Elevated BNP and NT-proBNP levels are used to detect CHF (Tobian, Sokoll, Tisch, Ness, & Shan, 2008). Research has been performed to investigate whether or not BNP and NT-proBNP could be used as serum markers to identify TACO in patients who develop respiratory complications during or following blood transfusion. Tobian et al, (2008) did a case-control study of 40 patients over a one year period. Sixteen of the 40 patients developed respiratory failure and were diagnosed with TACO. Twenty-four patients developed other types of transfusion reactions (allergic reactions, febrile nonhemolytic transfusion reactions, or no transfusion reaction at all) and were used as the control group. NT-proBNP measurement was performed prior to transfusion and also post-transfusion. The reference range or NT-proBNP is 0 to 125 pg per mL, the control group had a pre- transfusion NT-proBNP mean of 708 and it decreased to 618 post-transfusion. The patients with TACO had a mean 12,603 pre-transfusion and a mean of 12,238 post-transfusion. This information explains that the NT-proBNP can be helpful in the diagnosis of TACO, however is more helpful in explaining that patients who ultimately develop TACO are in a state of excess volume prior to transfusion.

Li et al., (2009) did a prospective cohort study of 115 critical care patients with development of pulmonary edema during or after transfusion in suspected TRALI and TACO cases to determine whether or not BNP and NT-proBNP levels were useful in differentiating TACO from TRALI. There results found that in general, elevated levels of BNP and NT-proBNP levels were higher in patients who developed post-transfusion cardiogenic pulmonary edema (TACO) compared to those who developed TRALI. However, there was a large overlap in values between the two groups and it was found that BNP and NT-pro-BNP is not specific to TACO and is not an accurate test to differentiate TACO from TRALI.

Pulmonary edema fluid testing for protein has been evaluated to help with diagnosing TRALI and TACO. Edema fluid to serum protein ratio has been used to determine whether it is cardiogenic or non-cardiogenic. The pulmonary fluid in TACO is a low-protein plasma filtrate and in TRALI is a high-protein plasma filtrate. Edema fluid to serum protein ratio of ≥ 0.75 has been used to distinguish TRALI from TACO. However, this has not been evaluated in a formal experiment and testing is limited to only intubated patients (Skeate & Eastlund, 2007).

Discussion

Interpretation

Transfusion-related acute lung injury (TRALI) is a very serious form of non-hemolytic transfusion reaction (NHTR). It is well-characterized and has serious outcomes if it is not recognized early and if improper treatments are initiated. The literature repeatedly states that the true incidence of TRALI is unknown because it has many of the same signs and symptoms as other NHTR's. Transfusion-associated circulatory overload (TACO) is another form of NHTR that has many of the same presenting signs and symptoms as TRALI. It is important for the SRNA and CRNA to be familiar with both TRALI and TACO so that accurate identification can

be made, as well as proper treatment. Accurate diagnosis of TRALI relies heavily on the ruling out of other NHTR's including TACO.

Most of the research that has been performed up to this point has been to try and fully understand the pathogenesis of TRALI. Research has shown that in most cases of TRALI the recipient has received donor human leukocyte antigen (HLA) antibodies that accumulate in the lung endothelium, damaging it, and causing increased permeability. In other cases of TRALI, a "two-hit" mechanism occurs, in which a patient experiences a "first-hit" such as severe infection, surgery, trauma, or massive transfusion which causes damage to the vascular endothelium. The "second-hit" that the patient experiences is caused by the transfusion of biological modifiers such as leukocyte antibodies, lipid priming molecules, cytokines, or endotoxins that develop in stored blood product.

TRALI differs from TACO in that the causes of TRALI lead to lung vascular endothelium damage leading to leaky vascular endothelium. TACO is the result of transfusion of excessive volume or more likely the transfusion of excessive volume in a short period of time. It seems the prevalence of TACO is also related to preexisting conditions such as cardiac dysfunction, renal impairment, and lung disease. The excessive volume coupled with these conditions lead to excessive intravascular volume that causes hydrostatic pulmonary edema.

Authors agree that to fully understand and differentiate TRALI from TACO the practitioner needs understand the pathogenesis of TRALI and TACO as well as the diagnostic criteria. Although TRALI and TACO present very similarly there are distinguishing factors that separate the two and it is best for the healthcare practitioner to rule out symptoms of TACO to accurately diagnose the patient with TRALI. The elderly, the very young, and those with a preexisting cardiac dysfunction are at higher risk for developing TACO. Patients who have a

positive fluid balance as demonstrated by an elevated PAOP (>18mmHg) or CVP (>12), jugular venous distention, or are experiencing significant diuresis are more likely fluid overloaded and are experiencing TACO.

The research has also examined whether or not elevated brain natriuretic peptide (BNP) and n-terminal pro-brain natriuretic peptide (NT-proBNP) levels used to detect CHF are useful for detecting TACO due to its similarities. The research has found that in cases of TACO these lab values are elevated, however these values were also elevated in some cases of TRALI. This limits the usefulness of BNP and NT-proBNP to just another factor to consider in distinguishing TRALI from TACO.

Research has also suggested testing the pulmonary edema fluid for the presence of protein which is seen in TRALI and not with TACO. The pulmonary fluid associated with TACO is a low-protein filtrate and the pulmonary fluid associated with TRALI is a high-protein plasma filtrate. Edema fluid to serum protein ratio of ≥ 0.75 has been a marker used to distinguish TRALI from TACO. Intubation is required to obtain an adequate sample of pulmonary fluid, which is a limiting factor in its usefulness. This information needs further evaluation for accuracy and its usefulness in differentiating TRALI from TACO.

Outcome/Dissemination

Following a comprehensive review of literature, the information was gathered and organized and presented to the anesthesia staff at Altru Health, Grand Forks, North Dakota and will be delivered to the attendees of the North Dakota Association of Nurse Anesthetists bi-annual meeting in Bismarck, North Dakota in October 2012. An evaluation tool will be distributed at the North Dakota Association of Nurse Anesthetists fall meeting to assess the quality of the presentation.

Implications for Nursing

Nursing Practice – Prevention of TRALI

Recent advances in the understanding of TRALI have led to many risk reduction strategies. The American Association of Blood Banks (AABB) has implemented protocols that require donors implicated in a TRALI case be evaluated for eligibility to donate. The donors are tested for presence of HLA Class I and II antibodies which have been the most implicated in cases of TRALI. Multiparous females are considered to be the highest at risk for HLA Class I and II antibodies. These donors are tested and those that test positive for leukocyte antibodies or test positive for cross-match between donor serum and patient leukocytes are deferred from donation of plasma containing blood products. A strategy that has been adopted in the U.K., since January of 2004, is the use of plasma containing products exclusively from male donors. The U.K. Serious Hazards of Transfusion (SHOT) data showed that TRALI cases associated with plasma rich components decreased from sixteen cases in 2003 to just three in 2005. Although, this has been a very effective strategy in reducing the risk of TRALI, there is sufficient evidence that shows nulliparous females have not tested positive for the HLA Class I or II antibodies. This would have a large effect on the supply of plasma containing blood product availability (Triulzi, 2009)

The use of fresher blood products to reduce the amount of biological modifiers such as leukocyte antibodies, lipid priming molecules, cytokines, or endotoxins that develop in stored blood products as well as using washed components has also been considered, however is not currently recommended. Another risk reduction strategy in development is the removal of

plasma from stored platelets and replacement with platelet additive solutions that would help decrease the risk of TRALI from platelet transfusions (Triulzi, 2009).

Nursing Practice - Treatment of a TRALI

Transfusion of blood products often starts while the patient is in the operating room under the care of the CRNA and SRNA. It is important to recognize the symptoms of TRALI and differentiate symptoms of TRALI from other transfusion type reactions and treat appropriately. A patient suspected of TRALI would show signs and symptoms of tachypnea, frothy pulmonary secretions, hypotension (less commonly hypertension), fever, tachycardia, cyanosis, rales on auscultation, and bilateral fluffy infiltrates on chest radiography. Also, the patient would less likely show signs of circulatory overload such as jugular venous distention, S3 gallop, elevated PAOP or CVP which is commonly seen with TACO. Signs and symptoms would commonly appear with in one to two hours from start of transfusion but can be seen up to six hours following transfusion (Triulzi, 2009).

In the event that TRALI is suspected, the CRNA or SRNA should stop the transfusion immediately; provide respiratory support with oxygenation and in most cases intubation and ventilator support. Diuretics offer little help because the pulmonary edema is not a result of fluid overload and in many cases these patients are in a euvolemic or hypovolemic state in which the diuretics will cause further hypotension. Cardiovascular support should be maintained or treated with fluids and medications as needed. There is no data suggesting that steroids are effective in the treatment of TRALI. Most patients will recover within 96 hours of the transfusion. It is important for the CRNA and SRNA to notify all disciplines involved in the care of the patient including surgeon, anesthesiologist, nursing and transfusion services. The blood component and

patient blood sample needs to be sent back to transfusion services to be worked up for the presence of lipid priming activity and/or neutrophil-activating factors (Triulzi, 2009).

Nursing Education

Continuing education for nurse anesthesia providers regarding TRALI as well as all transfusion reactions is necessary to ensure early, accurate recognition and prompt treatment to ensure safe and effective outcomes for the patient. This may be accomplished by reviewing current evidence based literature and frequently attending educational conferences.

Nursing Policy and Research

Health care institutions have been developing policies and procedures to ensure patient safety as well as practice guidelines for healthcare providers to deliver a high standard of care. These guidelines need frequent reviewing and updating to ensure the best evidence base clinical practice is being implemented. It is important for healthcare providers to follow these guidelines as a responsibility to their patients and profession.

Summary

Transfusion-related acute lung injury (TRALI) is a rare non-hemolytic transfusion reaction (NHTR) associated with transfusion of human leukocyte antigen (HLA) antibodies as well as other biological modifiers such as lipid priming molecules, cytokines and endotoxins that occur during the storage of blood products. These biological modifiers cause damage to the vascular endothelium within the lungs of patients causing the endothelium to become "leaky" resulting in edema and interfering with gas exchange. The presentation of TRALI is very similar to the presentation of transfusion-associated circulatory overload (TACO) in which the

pulmonary edema is a result of hydrostatic pressure from an increase in circulatory volume often in the presence of ventricular dysfunction.

There is no single test or factor that can easily differentiate TRALI from TACO so it is important for the SRNA and CRNA to be familiar and understand the pathogenesis of both TRALI and TACO. It is also important to understand how TRALI and TACO present similarly and how each differs from one another to be able to differentiate. It is also important for the SRNA and CRNA to understand how the treatment of TRALI differs from the treatment of TACO and that it is important for early identification and differentiation to ensure early and correct treatment and best outcomes for patients.

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