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Abstract

A review of the literature was conducted for the purpose of finding the benefits of using leukoreduced blood products and premedicating with antihistamine to prevent blood transfusion reactions in patients undergoing open-heart surgery. Four retrospective cohort studies, two meta-analyses, two observational studies, and three randomized controlled trials were examined with dates ranging from 2006 to 2016. Current literature indicates that leukoreduced blood products are superior to non-leukoreduced blood products and that their use can reduce both short and long term mortality risk in cardiac surgery patients. The use of leukoreduced blood products may also reduce the need for antihistamine premedication to prevent blood transfusion reactions in these patients since antigen-antibody reactions are responsible for the majority of acute and delayed transfusion reactions.

Blood Transfusion and Adverse Effects in Patients Having Cardiac Operations

Introduction

Patients having open-heart surgeries are the greatest consumers of blood products in the United States. These patients not only receive blood products but can also experience adverse effects that are deleterious to the open-heart operation itself (Horvath et al., 2013). With advances in medicine, many strategies have become available and implemented in most institutions to reduce blood transfusion during cardiovascular surgeries. These plans include normo-volemic hemodilution techniques, use of antifibrinolytic medications, cell salvaging techniques, low-hematocrit guidelines termed as restrictive measures, autologous transfusion, and the use of allogenic blood transfusion (Murphy et al., 2015). Despite these strategic measures, blood transfusion may still be the right treatment for blood loss and low hemoglobin in cardiac surgical patients. The overarching objective of cardiac surgery is a long term and healthy survival. However, the challenge is balancing the use of blood transfusion while reducing complications at the same time. A review of the literature reveals that leukoreduced blood products should be used in surgical patients, particularly in those having open-heart operations. Findings also show that blood conservation strategies are the best approach to decrease the needs for allogenic transfusion and reduce morbidity and mortality in cardiac surgery patients.

Literature Review

Several studies have unequivocally proven that blood transfusions are not without risk. Alloimmunization, for instance, is one of the risks associated with blood transfusion therapy. It leads to hemolytic reaction, renal failure and can be fatal. Alloimmunization is an immune response to foreign antigens. Although ABO, Rh D compatibility through cross matching of allogenic products reduces some risks of alloimmunization, there is still an array of free standing

factors that can provoke the formation of harmful antibodies in blood recipients. The presence of a spleen, genetic factors, red blood cell damage, and donor leukocytes are potential causative factors for alloimmunization during blood transfusion (Christopher, Tormey, & Shaz, 2014).

The spleen involves the work of both innate and adaptive immunity where the two systems collaborate to defend the body against pathogens. By definition, innate immunity is the body's first line of defense and therefore able to mobilize within minutes in the presence of a foreign antigen. Adaptive immunity, also referred to as acquired immunity, has an initially delayed response to foreign antigens; unless the host has been previously exposed to similar antigens, then the response can be immediate and amplified. Adaptive immunity further divides into two types: humoral and cell-mediated immunity, both of which play an important role in alloimmunization during a blood transfusion. Humoral immunity is facilitated by B-lymphocytes (B-cells) and functions effectively against extracellular microorganisms and toxins, while cell-mediated immunity is arbitrated by T-lymphocytes (T-cells) and serves in the destruction of intracellular pathogens (Porth, 2014). The spleen harbors some of those B-cells especially the memory B-cells, whose primary function is to mount a vigorous second immune response with re-exposure to specific antigens. Vaccination is one example of memory B-cells' function.

Researchers have investigated the spleen's functionality and related implications on blood transfusion recipients and found intriguing results. According to Hendrickson, Christopher, Tormey, & Shaz (2014), subjects in both animal and human studies subjects with previous splenectomy demonstrated higher rate in red blood cell antibody production. Those patients can mount a significant secondary immune response to red blood cell antibodies. The spleen functionality issue is more common in patients with thalassemia anemia who needed frequent blood transfusion therapy. It will continue to be a difficult task, however, to foresee and

protect patients that may have a greater risk for developing alloimmunization complications with a blood transfusion during cardiac surgery without an enhanced risk stratification screening tool preoperatively.

Genetic factors outside of ABO grouping compatibility can also predispose certain patients to alloimmunization. A mathematical model used to predict responders and non-responders to red blood cells antigens in both adult and pediatric patients, found there is a 30% chance of producing additional alloantibodies with blood transfusion in responder patients (Christopher, Tormey, & Shaz, 2014). Furthermore, patients with red blood cell defects such as sickle cell disease, malaria, and those with hemoglobinopathies are at increased risk for alloimmunization. Studies reveal that the occurrences of red blood cell alloantibodies to be as high as 35% in these patients (Christopher, Tormey, & Shaz, 2014). It is recommended that these patients be further screened through phenotype-matching for other types of antigens not routinely tested before blood transfusion. Some other antigens known as limited-phenotype such as C, E, K, and extended types can be matched so that predisposed patients can selectively receive specific red blood cells. The process of specific phenotyping is difficult and may even be logistically unrealistic because few institutions offer this service, and it can be costly for that same reason. However, in mice, as well as in human studies, phenotype-matched red blood cells reduce the rate of alloimmunization response from 34% to 7% (Christopher, Tormey, & Shaz, 2014). Another disease factor that affects red blood cells is active state of inflammation and infection. Patients with active bowel inflammatory disease at the time of transfusion have a higher risk for developing blood transfusion reactions (Christopher, Tormey, & Shaz, 2014).

Patients undergoing cardiac surgeries receive more allogenic blood products than any other category of surgical patient, excluding trauma (Murphy et al., 2015). These groups include

adult patients having coronary artery bypass graft (CABG) and valve replacement surgeries. Hospitals have adopted many strategies aimed at reducing the necessity for blood transfusion in cardiac surgery patients. The variability of blood transfusion rates in cardiac patients in the United States ranges from 85% to 93% (Murphy et al., 2015). Some of the factors leading to these differences in rates can be explained by many variations that exist in clinical practice among different health institutions. Some hospitals follow intuitional established protocol for transfusion threshold. Conversely, in some hospitals, it can simply be a provider's preference in addition to the patient's physiologic needs that may guide the decision to transfuse.

A large annual number of allogeneic blood transfusions are expected to occur in most major cardiovascular centers during both emergency and non-emergency cardiac surgery. Murphy et al. (2015) conducted a randomized controlled trial involving 2003 subjects to compare outcomes on restrictive versus liberal hemoglobin thresholds for blood transfusions in cardiac patients. A restrictive threshold, according to the study, is related to hemoglobin level less than 7.5 gm/dl, whereas a liberal threshold is defined as hemoglobin level greater 9 gm/dl. Primary outcomes studied within three-months post randomization included infection and ischemic events, which lead to myocardial infraction and acute kidney injury. More deaths were reported in the restrictive threshold group 4.6% versus the liberal threshold group that reported 2.6%, (hazard ratio =1.64), (95% CI, 1.00 to 2.67; P = 0.045). Those results are significant and prove that cardiac patients do benefit from blood transfusion. The authors also found that for 30-day mortalities, there were no clinically significant differences between the two groups regarding total costs and morbidity. However, the study lacks heterogeneity due to data collection inconsistency. More data was obtained from the restrictive group versus the liberal group 35% versus 33% respectively which could affect the validity of the results.

However, there are best practice guideline recommendations based on hemoglobin thresholds on when to initiate blood transfusions, as well as new methods for blood conservation strategies. Research indicates that perioperative blood conservation strategies (BCS) in patients having aortic valve surgery decrease the need for blood transfusion (Yafee et al., 2014). Those researchers initially conducted a controlled trial over a three-year period in a single large medical center in the U.S on 748 adult patients undergoing aortic valve replacement (AVR) surgery. They then retrospectively reviewed data prior and after the implementation of BCS for outcomes such as hospital deaths, major complication of respiratory failure, renal failure requiring dialysis, and sepsis. Their blood conservation methods principally revolved around patients' physiologic needs rather than initially establishing protocols for blood transfusion. According to Yafee et al. (2014), their selected method for treatment of hypotension related to anesthetics were vasopressors rather than fluid; providers were also educated to tolerate anemia based on individual patient hemodynamics. They also minimized hemodilution by using select cardiopulmonary bypass circuits with smaller diameter tubing. This particular study is of interest because the multidisciplinary team composed of surgeons, anesthesia providers, perfusionists and others was on board with the research protocol and plans. Earlier methods of blood conservation strategies for cardiac surgery patients were preoperative hemodilution, use of erythropoiesis-stimulating agents, and the utilization of autologous blood (Yafee et al., 2014). When comparing pre-and-post-BCS, Yafee et al. (2014) reported a decrease from 82.9% to 68% ($p<0.01$), a significant reduction in blood transfusion, as shown in Table 1.

Table 1

Effect of Blood Conservation on Perioperative Hematocrit Levels and Blood Product Utilization

All AVR Patients (N=778)			
Variables	Pre-RBCs (n=391) No. %	Post-RBCs (n=387) No. %	p-Value
Incidence of RBC transfusion			
Any RBCs	324 (82.9)	263 (68.0)	<0.01
≥ 2units	283 (72.4)	210 (54.3)	<0.01
Perioperative	280 (71.6)	202 (52.2)	<0.01
≥ 2 units	232 (59.3)	147 (38.0)	<0.01
Postoperative	212 (54.2)	184 (47.5)	0.06
≥ 2 units	139 (35.5)	108 (27.9)	0.02
Hematocrits %			
	36.5 ± 5.7	36.4 ± 5.8	>0.9
Lowest during CPB%	19.3 ± 10.5	24.2 ± 6.2	<0.01
Last on CPB%	21.7 ± 11.7	27.3± 6.8	<0.01
First postoperative %	32.9 ± 4.1	32.8 ± 4.9	0.7

Note: Continuous data are presented as mean ± standard deviation and categorical data as number (%). AVR = aortic valve replacement; BCSs = blood conservation strategies; CPB =cardiopulmonary bypass; RBC= red blood cell.
Adapted from "Management of blood transfusion in Aortic valve surgery" Impact of a blood conservation strategy, by Yafee et al., 2014. *The Annals of Thoracic Surgery*, *97*(1), 95–101. doi:10.1016/j.athoracsur.2013.09.057

The next tabulated results in Table 2 show there was no clinical significance of major complications in patients who received red blood cells over two units compare to those who did not receive blood based on the new BCS.

Table 2

Effect of Blood Conservation on Patient Outcomes

Variables	Pre-BCS	Post-BCS	p-Value
Hospital mortality	2.6%	3.4%	0.5
Major complications	9.0%	10.9%	0.4
Renal failure on dialysis	4.6%	4.7%	> 0.9
Respiratory failure	9.8%	11.3%	0.6
Sepsis/endocarditis	1.7%	0.3%	0.07

Note: BCSs = blood conservation strategies.
Adapted from "Management of blood transfusion in Aortic valve surgery" Impact of a blood conservation strategy, by Yafee et al., 2014. *The Annals of Thoracic Surgery*, *97*(1), 95–101. doi:10.1016/j.athoracsur.2013.09.057

According to recent data, patients undergoing aortic valve replacement surgeries received the highest percentage of blood transfusion among cardiac surgery patients 80% versus 20% for CABG. Methods of blood conservation strategy suggested by Yafee et al. (2014) can be efficient for blood allocation and cost control benefit in this group of patients. Blood transfusion is costly to both patients and hospitals; the new BCS trials resulted in an annual cost saving benefit of $339,522 for New York University Langone Medical Center (Yafee et al., 2014). Despite the low transfusion rate in the post-BCS group, patients did not have significantly better outcomes,

and perhaps did a little worse in the immediate post-operative period than those who received blood in the pre-BCS group as shown in Table 2.

The Case for Blood Transfusion in Cardiac Surgery Patients

During cardiac surgeries, patients receive blood transfusions for many reasons. Some are for uncorrected preoperative anemia, intraoperative blood loss that causes hemostatic instability, hemorrhagic complications, and to prevent postoperative anemia-related complications. Oxygen delivery to tissues is paramount during any cardiovascular operation and is thereby the primary reason for blood transfusions in these patients. Optimizing hemoglobin levels to expand oxygen delivery is key to adequate organ perfusion (van de Watering, 2013). According to the World Health Organization (WHO, 2011), anemia is defined by a hemoglobin of less than 13.0 gm/dl for men, and less than 12 gm/dl for women. Cardiac patients tend to be older with other comorbidities; anemia is a common diagnosis in this population. Hence, anemia is a marker for poor outcomes in the cardiac patients having surgery (van de Watering, 2013). Anemic patients are likely receiving blood transfusion during cardiac surgery and likely to developing an ischemic stroke intraoperatively (van de Watering, 2013). Moreover, a large majority of patients presenting for cardiac surgery are already at their limit in terms of cardiac reserve and may not be able to afford a lower hemoglobin level to sustain organ perfusion.

Red blood cells flow to capillary beds delivering oxygen to muscles and tissues in exchange for carbon dioxide and other metabolic waste products. Red blood cells represent nearly 40-45% of human's total blood volume, a much-needed amount of oxygen carrying capacity (Porth, 2014). The formula for oxygen delivery (DO2) during cardiopulmonary bypass is as follows: DO2 = (pump flow rate x (hemoglobin concentration x hemoglobin saturation x 1.36) + (0.003 x arterial oxygen tension)), (Murphy, Hessel, & Groom, 2009, p. 404). Increasing

the pump flow rate will increase perfusion and oxygen bound to hemoglobin, which is directly related to the amount of hemoglobin available. Hemoglobin level has the greatest impact on oxygen delivery to tissue as implied by the formula. Whenever oxygen-carrying capacity is reduced, especially in cardiac patients, tissue hypoxia becomes imminent.

Some cardiovascular centers have stringent criteria for blood transfusions in cardiac patients. The restrictive approach for blood transfusion is typically a hemoglobin level of less than 8 gm/dl and hematocrit of less than 25% (Canton, 2016). For cardiac patients, anemia is associated with higher mortality rates than in non-anemic patients. In the study conducted by van de Watering (2013), its explained that every decrease of 1 gm/dl in hemoglobin concentration is associated with a 13% increase in cardiovascular events and 22% increase in all-cause mortality. These findings theorized the necessity for blood transfusion during cardiac surgery. Uniformly, the optimal perfusion outcome should be achieved with minimal harm to the patients, both short- and long-term.

Leading Causes of Mortality and Morbidity from Blood Transfusions

According to recent data from the Food and Drug Administration (FDA), the following transfusion risks are the leading causes of mortality and morbidity to transfusion recipients: bacteria or viral contamination, ABO-mismatched blood products, and transfusion-related acute lung injury (TRALI). Bacterial or viral contaminated blood products pose the biggest risk of systemic infection in patients. The risk for sepsis, however, is greater in platelet infusions than red blood cell transfusions, because platelets are stored at 20-24°C and are only usable for five days. In contrast, red blood cells are stored at 4°C and can be stored for up to 42 days in the United States. Although there are several pathogenic bacteria, such as *Yersinia enterocolitica*, that grow at 4°C, the incidence is very rare (Alexander et al., 2015).

Also, the current bacterial screening across blood banks centers is very effective. The implementation of rapid and efficient bacterial screening of FDA approved irradiation-based pathogen reduction methods, has been successful in reducing the risk of bacterial infection. The pathogenic reduction rate in blood products in the U.S is over 90% (FDA/CBER, 2016). There are remaining concerns regarding viral and bacterial transmission through blood transfusions. For example, emerging infectious diseases such as Zika virus, and even some unknown emerging pathogens, may not be immediately screened in donor blood. Overall, the process of blood collection and preparation for transfusion is safe, and products are screened for most microorganisms that can cause debilitating illness. Non-infectious transfusion reactions account for the majority, >80% of blood transfusion reactions (Racine, Carvajal, & Rodriguez, 2015). Blood product shelf-life durability is made possible through addition of soluble protein additives, such as citrate-based phosphatase and adenine, and do not increase mortality in recipients (Kleiman, Silvergleid, & Tirnauer, 2016).

A meta-analysis conducted by Alexander et al. (2015) found no impact on mortality in those who receive fresher versus older red blood cells. That review consisted of 12 randomized controlled trials that enrolled over 5000 hospitalized patients. It should be noted that the review included a broad range of patients from neonates to adults and included both surgical and medical patients. Fresher red blood cells were defined as having a storage life of fewer than 7-21 days and older red blood cells were described as having a storage life of 22-42 days (Alexander et al., 2015). The authors, however, did find an increase in nosocomial infection rate in neonates and cardiac patients infused with fresher red blood cells. In contrast to this study, prior observational studies have proposed that fresher units are superior to older units in reducing transfusion complications. The autors did not provide rationales for the increase in infection rate

in neonates who were transfused with fresher red cells. It is known that immunosupression is common in neonate who receive blood transfusion. Also, according to Quinn et al. (2015) fresher red blood cells are preferentially used in neonates because older red blood cells contain a higher concentration of potassium and lactate, thus may induce arrhythmias and cardiac arrest in neonates.

ABO-Incompatibility and Blood Transfusion Reactions

ABO and Rh D grouping and compatibility is routinely matched for recipients and is recommended for blood transfusion. ABO refers to a blood group system that is genetically determined in human blood. The grouping is as follows: A, B, AB, and O and represent antigens expressed on the surface of the red blood cells, or erythrocytes, and plasma (Perth, 2014). There is also the D antigen, which determines the Rh-positive type. Blood is compatible when the donor's antigens match that of the recipient's; no anti-A or anti-B antibodies will be exposed to the recipient’s antigens. Group O patients have non-functional red cell antigens and are therefore referred to as universal donors (Perth, 2014). It is safe to administer O Rh negative blood to any patients in case of an emergency if cross-matched blood is not available (AABB, 2014).

Health institutions across the United States have established universal safety protocols for blood transfusions to prevent administrative errors or misidentification, thus preventing ABO mismatching error. Level-one studies have demonstrated that ABO-incompatible blood causes a life-threatening acute hemolytic transfusion reactions. The delayed hemolytic reaction can occur up to ten days after receiving a blood transfusion. The pathological etiology is likely secondary to concealed antibodies in the patient's blood. The best practice is to transfuse patients with ABO-compatible and identical blood. In a practice, this is not always possible, and sometimes

lifesaving efforts necessitate non-identical but nearly compatible blood to be transfused during emergencies.

Universal donor blood O type can be safely transfused when matched or identical blood is unobtainable. An observational study over ten years by Pal et al. (2015) analyzed data from nearly 19,000 participants with blood groups A, B, and AB who received blood transfusions. They found no increased risk when non-identical red blood cells were transfused to blood type B or AB. However, the study revealed a trend in complications and an increased mortality rate only in patients with group A blood who received uncross-matched red blood cells. Patients with group O type were excluded in the study. According to Pal et al. (2015), group A blood type patients are more susceptible to adverse reactions and transfusion-related complications when they receive uncross-matched blood products. The mechanism for the increased sensitivity for reactions in group A patients is unclear and therefore warrants more research in this area.

Patients should be continuously monitored for signs of ABO incompatibility throughout the course of the transfusion. In anesthetized patients, these symptoms include hyperthermia, hypotension, decreased cardiac output, and hemoglobinuria (Despotis, Esby, &Lublin, 2008). Hypoxic patients may display signs of respiratory distress or circulatory overload. Patients may also become increasingly difficult to ventilate, develop bronchospasm, and increased peak airway pressure. Hypocalcemia in patients can also be a contributing factor from citrate toxicity after multiple blood transfusions. These signs and symptoms are non-specific and can be present in other transfusion-related complications.

Transfusion-Related Acute Lung Injury (TRALI)

TRALI is among the leading causes of transfusion-associated mortality; it is especially detrimental to the cardiac surgical patient. The incidence of TRALI is 1:1000 to 5000 blood

transfusions, with a mortality rate of five to ten percent of the general population. The mortality rate of TRALI is up to 13% higher in cardiac surgical patients (van de Watering, 2013). In a prospective case-controlled study by Vlaar et al. (2012), the incidence of TRALI in cardiac patients was associated with previously active systemic inflammation and neutrophil activation before transfusion was even administered. Since the onset of TRALI was approximately six hours after blood transfusion, that study may have some limitations and ambiguities as to what truly causes TRALI.

Until now, the pathological endpoint for TRALI has not been fully appreciated. Several possible causes may explain this dangerous phenomenon. One of the most studied topics is anti-leukocyte-antibodies in the donor's blood that get passively transfused, and binds to the recipient's antigen, specifically neutrophils. This one event can trigger overwhelming inflammatory responses that are detrimental to the pulmonary endothelium (Tao et al., 2009). A second relevant study from Fransen et al. (2009) examined 114 patients undergoing cardiac surgery and found a strong correlation between a peak in the concentration of pro-inflammatory mediators such as the interleukins, cytokines, neutrophil elastase, in allogeneic blood transfusion.

During cardiac surgery, capillary leakage due to inflammation also causes transfusion-associated cardiac overload (TACO) and causes pulmonary edema. In some instances, the rate of the transfusion may be faster than the patient's already compromised cardiac output, causing circulatory overload. This term is less discussed in the literature and can be interrelated with TRALI. Older patients with previous renal disease undergoing cardiac surgery are at greatest risk of TACO (van de Watering, 2013). According to the Short report in the UK, TACO represents 30% of morbidities and 70% of mortalities in transfused patients (Balton-Maggs, 2014).

Transfusion-related immunomodulation (TRIM) is another serious complication of blood transfusions in the cardiac patient. This transfusion reaction can be fatal and tends to occur more in cardiac patients. Similar to the TRALI theory, with TRIM, leukocytes are also a presumed factor. TRIM occurs as a result of an additional inflammatory insult by blood transfusion during cardiac surgery. The operation itself is a primer of pro-inflammatory mediators. The mechanism of action for this starts with components within most red blood cell units. Units prepared for transfusion contain killer-leukocytes, erythrocytes, residual platelets, and other active factors that are released during storage (Bilgin & Brand, 2011). It has been proposed that leukocytes derived from these red blood cell units induce immediate upregulation of inflammatory genes in vivo (Bilgin & Brand, 2011). Furthermore, leukocytes in blood products may act as stimulator cells, activating cellular immunity and antibody production. Leukocytes appear to be the punitive agents in blood transfusions, responsible for TRALI, TACO, and TRIM; the three most destructive transfusion-related injuries in cardiac patients.

The Role of Antihistamine in Preventing Inflammation in Transfusion Reactions

Literature reveals that the use of prophylactic medications prior to blood transfusion is no longer standard of practice. Premedication, including mainly antihistamines, antipyretics, and diuretics, previously, was estimated to occur in 50% to 80% of transfusions (Fry et al., 2010). In current practice, premedication is not common and is mostly reserved for use in hematology and oncology patients, who require frequent transfusion and are prone to developing reactions. Premedication, especially antihistamines, can be effective in preventing febrile non-hemolytic transfusion reactions (FNHTRs), as well as allergic transfusion reactions (ATRs). Fry et al. (2010) conducted an observational retrospective chart review of 3,088 eligible transfused patients. The authors studied the rate of use of premedication to prevent FNHRT, ART, and

TACO in blood recipients. The study revealed that less than 2% of patients received premedication for the prevention of FNHRT, ART, and TACO before blood transfusion. In six studies previously published regarding the use of premedication to prevent blood transfusion reactions, only one retrospective study suggested that premedication was linked to fewer transfusion reactions (Fry et al., 2010). The trend in those studies shows that premedication to prevent transfusion reaction is no longer the standard of practice. The main reason for this decline in practice is the effectiveness of leukoreduced blood product.

While reviewing the literature on the use of premedication in cardiac surgery patients to prevent blood transfusion reactions, an observation was made regarding the antihistamine cimetidine. Although antihistamines are not proven to decrease adverse events related to blood transfusions, cimetidine, a histamine type-two inhibitor, has been shown to enhance cellular immunity in surgical patients undergoing cardiopulmonary bypass operations. In a randomized controlled trial of 40 patients undergoing cardiac surgery involving cardiopulmonary bypass, cimetidine was effective in reducing pro-inflammatory mediators and preserving cell-mediated immune responses (Tayama et al., 2016). An earlier study also reported that perioperative administration of cimetidine "inhibited the reduction of natural killer cell activity on post-operative day one, in patients who had cardiopulmonary bypass operations" (Tayama et al., 2016, p. 1948). In comparison, those same pro-inflammatory mediators discussed in the previous section in this paper are responsible for transfusion-related injuries, such as TRALI, and TRIM in the same group of patients. Cimetidine may be able to provide double benefits and indirectly protect cardiac surgery patients against transfusion-caused inflammatory mediators.

A retrospective study reported by Bjursten et al. (2015) enrolled nearly 10,000 patients having open-heart surgeries over a period of 12 years and found that transfusion of a small

amount of non-leukoreduced blood was associated with a decrease long-term survival. The study also reported findings on other heterogeneous contributing factors in blood transfusions associated with decreased short-term survival in cardiac patients. That study coalesces with previous studies that also reported an increase in infection rates as well as an increase in short-term mortality in cardiac patients transfused with non-leukoreduced red blood cells. A recent study reveals an increase in one-year mortality rate in patients who received one to two units of non-leukoreduced red blood cells without an increase in mortality rate after one year (Bjursten et al., 2015).

Leukoreduced blood products also reduce the risk of FNHTRs, thereby eliminating the need for premedication with antihistamines. Anti-human leukocyte antigens (HLA) are primarily responsible for FNHTRs in transfused patients. In an animal study conducted by Tao et al. (2009) leukocyte depletion was shown to mitigate the occurrence of acute lung injury caused during cardiopulmonary bypass surgery (CPB). That particular study was a randomized controlled trial involving 18 dogs undergoing CPB. The subjects were separated into three groups: leukocyte depletion filter for ten minutes (LD-S), leukocyte-depletion for the duration of the CPB (LD-T), and a control group. They evaluated the effectiveness of leukocyte depletion during CPB on lung function by measuring pulmonary vascular resistance (PVR) and oxygen index to assess inflammatory response. The authors found significantly lower postoperative neutrophil counts, better PVR numbers, and higher oxygen index in both LD-S and LD-T groups versus the control group (Tao et al., 2009). PVR was even better in the LD-S group (short term) leuko-depletion technique, showing that accumulation of leukocytes in the filter can also be activated, and enter circulation over time. Given this information, it is rational to speculate that

the leukocyte-depletion method may not only protect patient's lungs against inflammatory insults from a blood transfusion, but also acute lung injury from CPB.

Ample evidence indicates that leukoreduced blood products provide a level of protection to patients. One meta-analysis conducted by Racines, Carvajal, & Rodriquez (2015) reviewed 13 randomized controlled trials to look at the effect of leukoreduction of red blood cells on preventing TRALI, infection, febrile non-hemolytic transfusion reactions, infection from any cause, and death due to any cause. Five out those thirteen trials that were specific to cardiac surgery patients reported inconclusive results. They have found little evidence to argue in favor or against leukoreduction methods for blood transfusion (Racines, Carvajal, & Rodriquez, 2015). In the same meta-analysis, nine other trials involving a broader group of surgical patients found lower risk of severe sepsis and respiratory failure with leukoreduced blood product (Racines, Carvajal, & Rodriquez, 2015). Method and frequency of the use of leukoreduced blood varies widely among different health institutions. It is estimated that >80% of hospitals in the United States use leukoreduced blood product, while others do not as it is not an FDA requirement (Ryder, Zimring & Hendrickson, 2014). Some health centers ration leukoreduced blood by using a selective strategy because the process of leukoreduction proves to be too costly. Moreover, the collection and processing procedure can affect the efficiency of leukoreduction. There is no standardized modus among health centers to process blood when it comes to additive such as anticoagulant, preservative solution, holding time, and the type of technology used for leukoreduction (Ryder, Zimring & Hendrickson, 2014). Nevertheless, limited trials are available to favor one method over another. In a cost-driven health care system, the most economical method will prevail. According to Racines, Carvajal, & Rodriguez (2015), the annual cost of leukoreduction process and implementation in the U.S is approximately 600 million dollars.

Discussion

Leukocyte depletion methods have been tested since the early 1970s. At that time, filters were among the first tools used in this procedure. Several approved methods are available to efficiently achieve leukoreduce erythrocytes. The process can be done at the time of collection, during storage at the blood bank, or post-storage by the clinician at the bedside through the use of a high-efficiency FDA-approved filter (Sharma & Marwaha, 2010). According to current literature, the pre-storage leukoreduction method is the most popular. A fresh unit of whole blood contains approximately 10^9 leukocytes. According to the American Association of Blood Banks (AABB), the standard for leukoreduction is 10^6, a three-time log reduction from the original whole blood. This translates to an efficiency of 99.9% reduction rate in leukocyte numbers, with at least 85% of the original red blood cells present (R. R. Sharma & Marwaha, 2010). The FDA has a slightly lower standard than that of the AABB. The cost of leukocyte depletion of one unit of whole blood is approximately 30 US dollars (Racines, Carvajal, & Rodriquez, 2015). According to that same article, methods of leukoreduction do not provide the same efficacy; some are only able to provide a reduction of less than 90% or a one to two-time log reduction. Even small amounts of unfiltered leukocytes are enough to cause severe transfusion reactions. Fortunately, the leukoreduction process has been mostly taken away from the provider in the operating room, and the widely accepted method is pre-storage at the blood bank. However, it can also be done in vivo during cardiopulmonary bypass. The required blood filter at the time of transfusion, usually a 150 to 260-micron filter, is used for the removal of blood clots and clumping particles, and not for leukocytes reduction (AABB, 2014). Moreover, bedside leukoreduction of blood products may cause an abrupt drop in blood pressure in some patients, especially if they are taking an angiotensin-converting enzyme inhibitor (AABB, 2014).

In an observational study by Bilgin & Brand (2011) a 33% reduction in hospital mortality rate was found when leukoreduced red blood cells were used in cardiac surgery patients. The observational study by van de Watering (2013) also found a 50% reduction in 60-day mortality in that same patient population, with the use of leukoreduced red blood cells. To restate the significance of leukocytes in this paper, they are specialized cells classified into granulocytes and agranulocytes involved in innate immunity that are quick to mount an extensive inflammatory response against foreign pathogens. That same protective mechanism can be catastrophic to other organs, especially the cardio-pulmonary and renal system.

Limitations

Limitations that must be considered: many of the level-one controlled trials were conducted outside of the U.S and may have different practice standards and regulations regarding blood administration. Having a different level of practice may skew research to a conclusion of worse or better outcomes. Although, studies that involved surgical patients were mostly selected those with larger sample size that also included some medical, hematology and cancer patients. Furthermore, potential for bias existed because there was no distinction in procedure type to delineate the ones that use more transfusions and carry higher mortality rates over another. Heart operations may involve different types of procedures, such as coronary artery bypass grafting, aortic valve replacement, mitral valve replacement, plus a combination of both bypass grafting and valve replacement. Additionally, many observational studies on this topic lack the statistical power to adequately detect significant results on the net effects of leukoreduced blood in patients. However, strong evidence in the literature promotes the use of leukoreduced blood products in cardiac surgical patients and warrants standardized practice in this area.

Leukoreduction when properly implemented can prevent many of the harmful complications associated with blood transfusion.

Recommendation for Practice

Premedication is not necessary as a routine practice for the prevention of blood transfusion reactions. Patients with chronic allergic reactions should receive washed red blood cells, if available. The washing process prevents the passage of residual plasma proteins, thus, decreasing or in some cases eliminating the amount of IgA antibodies expressed in the donor plasma (AABB, 2014). IgA deficiency although relevant, is a rare cause of anaphylactic reaction to blood transfusion (Despotis, Esby, & Lublin, 2008). Common allergic reactions, such as urticaria and post-transfusion purpura, can be dramatically reduced with leukoreduced blood. Transplant patients should receive irradiated blood products to mitigate the risk of graft-versus-host disease. There is not sufficient clinical evidence to replace irradiated blood products with leukoreduced blood in transplant patients, although the latter option provides excellent overall protection as previously discussed. Under the new published guidelines by the AABB, a restrictive hemoglobin threshold of 8 gm/dl is recommended for transfusion during cardiac surgery (Carson, 2016). The new blood conservation strategy can also be implemented to diminish blood transfusion in cardiac surgery patients, where providers can tolerate a hemoglobin level lower than 8mg/dl without compromising hemodynamic status. Risk stratification should also be improved by not only assessing a patient's physiologic and physical status, but also by obtaining critical genetic background information. Nonetheless, as blood transfusion continues to be the life-saving measure for some of those patients, remedies to mitigate related complications should also be implemented.

Conclusion

Some groups of patients, notably those undergoing cardiac surgeries, are more vulnerable than others to having severe, and even lethal, transfusion-related complications. Blood transfusion related complications may present spontaneously during surgery, in the immediate post-operative period, at discharge, or can persist for weeks after discharge. With anesthesia in particular, many interventions do not end in the operating room and can have enduring negative effects on patients' recovery efforts. Although providers are responsible for adhering to institutional protocols when administering blood products, a comprehensive approach is also necessary when making that critical decision. The optimal goal of cardiac surgery is long-term and healthy recovery for each patient. It starts with every surgical team member. Anesthesia providers must ensure the appropriate selection of leukoreduced blood be made available for cardiac surgery patients. Finally, they must continuously be weighing risk-versus-benefit for each patient and should take steps to implementing current evidence-based practice for blood transfusion in the operating room theatre.

References

American Association of Blood Banks. AABB, (2014). *Circular of information for the use of human blood and blood components*. Retrieved from http://www.aabb.org/tm/coi/Documents/coi1113.pdf#search=ABO%20compatibility

Alexander, P. E., Barty, R., Fei, Y., Vandvik, P. O., Pai, M., Siemieniuk, R. A. C., Guyatt, G. H. (2015). Transfusion of fresher vs older red blood cells in hospitalized patients: A systematic review and meta-analysis. *Blood*, *127*(4), 400–410. doi:10.1182/blood-2015-09-670950

Bilgin, Y., & Brand, A. (2011). Transfusion-related Immunomodulation (TRIM): A Second hit in an Inflammatory cascade? *Vox Sanguinis*, *95*, 261–271. Retrieved from https://openaccess.leidenuniv.nl/bitstream/handle/1887/17880/04.pdf?sequence=7

Bjursten, H., Dardashti, A., Bjork, J., Wierup, P., Algotsson, L., & Ederoth, P. (2015). Transfusion of Sex-mismatched and non-leukocyte-depleted red blood cells in cardiac surgery increases mortality. *The journal of thoracic and cardiovascular surgery*, *152*(1), 223–232.

Bolton-Maggs, P. H. B. (2014). Bullet points from SHOT: Key messages and recommendations from the annual SHOT report 2013. *Transfusion Medicine*, *24*(4), 197–203. doi:10.1111/tme.12142

Carson, J. L. (2016). Clinical practice guidelines from the AABB. *JAMA*, *316*(19), 2025–2035. doi:10.1001/jama.2016.9185

Despotis, G., Esby, C., & Lublin, D, M. (2008). A review of transfusion risks and optimal management of perioperative bleeding with cardiac surgery. *Transfusion*, 48, 2S-30S. doi: 10.1111/j.1537-2995.2007.01573.x

U.S Food and Drug Administration/Center for Drug evaluation and Research. FDA/CBER, (2016). *Bacterial risk control strategies for blood collection establishments and transfusion*

services to enhance the safety and availability of Platelets for transfusion draft guidance for industry. Retrieved from http://www.fda.gov/downloads/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/Blood/UCM425952.pdf

Fry, J., Catherine, D., Arnold, D. M, Clase, C. M, Holbrook, A. M., Traore, A. N., Warkentin, T. E., & Heddle, N. (2010). Transfusion premedication to prevent acute transfusion reactions. *Transfusion*, *50*(8), 1722–1730.

Hendrickson, J. E., Tormey, C. A., & Shaz, B. H. (2014). Red blood cell Alloimmunization mitigation strategies. *Transfusion Medicine Reviews*, *28*(3), 137–144. doi:10.1016/j.tmrv.2014.04.008

Horvath, K. A., Acker, M. A., Chang, H., Bagiella, E., Smith, P. K., Iribarne, A., Blackstone, E. (2013). Blood transfusion and infection after cardiac surgery, *95*(6). Retrieved from https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3992887/

Jotted, J. R., Drakes, S. G., Hammond, H., & Everett, G. (2010). Effect of blood product transfusion- induced tolerance on incidence of cardiac allograft rejection. *Transplantation proceedings*, *42*, 2687–2692.

LMG van de Watering, Y. B. (2013). Complications after cardiac surgery due to Allogeneic blood transfusions. *Journal of Clinical & Experimental Cardiology*. doi:10.4172/2155-9880.s7-005

Murphy, G. J., Pike, K., Rogers, C. A., Wordsworth, S., Stokes, E. A., Angelini, G. D., & Reeves, B. C. (2015). Liberal or restrictive transfusion after cardiac surgery. *New England Journal of Medicine*, *372*(11), 997–1008. doi:10.1056/nejmoa1403612

Pai, M., Cook, R., Barty, R., Eikelboom, J., Lee, K.-A., & Heddle, N. (2015). Exposure to ABO-nonidentical blood associated with increased in-hospital mortality in patients with group A blood. *Transfusion*, *56*(3), 550–557. doi:10.1111/trf.13376

Porth, C. (2014). *Essentials of Pathophysiology (9th ed): Concepts of altered states*. Philadelphia, PA, United States: Lippincott Williams and Wilkins.

Quinn Kerry, Q. M.-K. (2015). Neonatal transfusion models to determine the impact of using fresh red blood cells on inventory and exposure. *Blood transfusion, 13*(4), 595-599. doi:10.2450/2015.0300-14

Racines , S. D., D, O., Carvajal , M. A., & Rodriguez, A. (2015). *Leukoreduction for the prevention of adverse reactions from allogeneic blood transfusion (Review)The Cochrane Collaboration*. doi:10.1002/14651858.CD009745.pub2.

Ryder, A. B., Zimring, J. C., & Hendrickson, J. E. (2014). Factors influencing RBC alloimmunization: Lessons learned from murine models, *41*(6), doi:DOI: 10.1159/000368995

Sharma, R., & Marwaha, N. (2010). Leukoreduced blood components: Advantages and strategies for its implementation in developing countries. *4*(1). Retrieved from https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2847337/

Tao, K., An, Q., Lin, K., Lui, R., & When, X. (2009). Which is better to preserve pulmonary function: short or prolong leukocyte depletion during cardiopulmonary bypass term. *Journal of thoracic and cardiovascular surgery, 138*, 1385–91.

Tayama, E., Hayashida, N., Fukunaga, S., Tayama, K., Takaseya, T., Hiratsuka, R., & Aoyagi, S. (2016). High-dose cimetidine reduces pro-inflammatory reaction after cardiac surgery with cardiopulmonary bypass. *The Annals of Thoracic Surgery*, *72*(6), 1945–1949. doi:10.1016/S0003-4975(01)03225-8

Yaffee, D. W., Smith, D. E., Ursomanno, P. A., Hill, F. T., Galloway, A. C., DeAnda, A., & Grossi, E. A. (2014). Management of blood transfusion in Aortic valve surgery: Impact of a blood conservation strategy. *The Annals of Thoracic Surgery*, *97*(1), 95–101. doi:10.1016/j.athoracsur.2013.09.057