REVIEW ARTICLE

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Complications of Blood Transfusion in Critical Situation: A Concise Overview

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INTRODUCTION

The complications associated with transfusion of blood products in the intensive care unit are under-diagnosed and could be associated with significant morbidity and mortality. They range from innocuous febrile reactions to hepatitis, human immunodeficiency virus (HIV), major incompatibility reactions and sepsis with life-threatening sequel. On the bright side, with the advent of new screening methods, the incidence of HIV and hepatitis C transmission has dropped dramatically. In this review, we intend to summarize the commonly encountered complications associated with blood transfusion for the critical care staff. The first part deals with the complications of transfusion pertaining to each component of the blood i.e. granulocytes, red cells, platelets, and serum. The second part, deals with infection-related and other uncommon complications of transfusion.

GRANULOCYTE INCOMPATIBILITY REACTIONS

Acute Febrile Reaction:

The most common cause of a febrile reaction during blood transfusion is caused by granulocyte antibodies to donor granulocytes during transfusion. The reaction can present with fever, chills, and facial erythema with an onset of 30 to 60 minutes after transfusion (1). This reaction can be seen in patients with prior transfusion and multi-parity.

Treatment is supportive. Transfusion is stopped or slowed and acetaminophen is given. Although depletion of blood from leukocytes (leukoreduction) has been advocated by some as a means of prevention, the data is insufficient and strong clinical trials are needed. In a review by Lane (2), the established indications for leukocyte-reduced blood components included: a) prevention of recurrent nonhemolytic febrile transfusion reactions to red blood cell transfusions, and b) prevention or delay of alloimmunization to leukocyte antigens in selected patients who are candidates for transplantation and transfusion on a long-term basis. Leukocyte reduction as a means to prevent transfusion- related acute lung injury (TRALI) or to prevent transfusion-related graft versus host disease is not indicated (see below).

TRALI

TRALI is a serious condition and is a cause of acute respiratory distress syndrome (ARDS) or non-cardiogenic pulmonary edema. The presentation

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consists of fever, dyspnea, and bilateral infiltrates on chest X-ray. It usually presents 1 to 4 hours post-transfusion, but at times it can be delayed for up to 40 hours (3- 5). Multi-parity is a risk factor.

TRALI can occur after transfusion of fresh frozen plasma (FFP), whole blood platelets, packed red blood cells (RBC), and cryoprecipitate. The occurrence is 1 in 5000 units of blood transfused.

The two major theories behind TRALI are:

a) HLA-specific antibodies present in donor serum-containing blood products react with recipient white blood cells (WBC) on specific sites. This reaction causes the release of granulocytic oxidative and non-oxidative products that disrupt the pulmonary endothelium, bringing about capillary leakage and increase in permeability. The blood source can be from multiparous female donors.
b) During blood storage, cell membranes of older blood cell components break apart and release biologically active lipids; these in turn activate circulating neutrophils which can subsequently stimulate acute lung injury (6).

Treatment of TRALI is mostly supportive (3- 5). As in other causes of ARDS, diuretics are not helpful. Steroids are shown to help in animal models. Approximately three-fourth require mechanical ventilation. Mortality is about 6 percent. Long lasting pulmonary complications are rare and most resolve within 3 to 4 days. If TRALI is proven as the cause of ARDS, the next transfusion is preferred to be autologous. Also, the packed RBC needs to be washed prior to transfusion to remove residual plasma as a source of antibodies (3- 6).

RBC Incompatibility Reactions

a. Hemolytic Reactions

There are two types of hemolytic reactions: major, which could have catastrophic consequences, and minor.

The major type is because of blood type (ABO) incompatibility in which a patient receives the wrong blood type. The most common cause is nursing, clerical, or blood bank staff error. The onset is rapid but at times may take an hour. The classical presentation includes renal failure, hemoglobinuria, bilirubinemia, elevated lactate dehydrogenase, positive direct Coombs test, shock, and ARDS. These are all features of massive intravascular hemolysis which are caused by complement fixing antibodies present in the recipient's serum (1).

Treatment is mainly supportive with volume resuscitation (crystalloid and colloids). If not done early, the mortality could be very high.

The minor hemolytic reaction is caused by Rh and other minor blood group incompatibility. Unlike major reactions, the minor reaction does not involve fixation of the complement pathway. The reaction can rarely cause extravascular hemolysis manifested by fever and hyperbilirubinemia (1). Treatment is usually supportive with administration of acetaminophen.

b) Delayed Transfusion Reaction

Unlike hemolytic reactions which present shortly after transfusion, the delayed transfusion reaction may take as long as a week or even longer before it is manifested. Since it is delayed, it is often missed by even an astute clinician. The incidence is approximately 1 in 500 transfusions.

The reaction is brought about by IgG antibodies that do not fix complement. The presentation is fever, elevated bilirubin, fall in hemoglobin count, jaundice, and hemoglobinuria, which are features of extravascular hemolysis (1). In a way, it resembles a minor hemolytic reaction with a very late presentation.

Platelet Incompatibility Reactions

The most common reaction is a febrile reaction which can be caused by granulocytes that have

contaminated the pool of platelets.

There is another serious rare and delayed reaction known as post-transfusion purpura which is triggered by sensitization to a foreign platelet antigen. Usually recipients have had a prior transfusion or pregnancy and harbor an antibody that attacks the patient's own platelets with transfusion of blood with platelets carrying the antigen. Subsequent thrombocytopenia and purpura result. Treatment involves plasma exchange or immunoglobulin infusion (1).

Plasma Incompatibility Reactions

The most common adverse effect of plasma transfusion is pruritis and skin erythema. A foreign protein in the donor's plasma provokes an IgE antibody response in the recipient's serum which is usually mild. Treatment involves slowing the transfusion and diphenhydramine.

A rare, albeit very serious, anaphylactic reaction can occur when the recipient is devoid of IgA in his/her plasma.The IgA in donor's plasma is attacked by recipient's anti- IgA antibodies, stimulating an anaphylactic reaction with hypotension, dyspnea, and chest pain. The incidence of IgA deficiency is 1 in 1000 in the normal population (1).

Infectious Disease Complications

This complication usually occurs during or within several hours after transfusion. It is mostly seen during platelet transfusion. But it can also occur with RBC transfusion. Platelets are stored at times for up to 5 days and can be an ideal environment for growth of bacteria.

Frequently, the affected patient presents with chills, fever, and hypotension. Infrequently the symptoms could mimic TRALI. At times the contamination can have grave consequences. In cases of severe systemic inflammatory response, ARDS and multi organ failure, mortality can be as high as 25%. It is estimated that with 4 million annual platelet transfusions in the US, 2000 to 4000 bacterial contaminations and 333 to 1000 cases of severe sepsis may be encountered (7).

Contamination is caused by the release of endotoxin which is proportional to the bacterial burden in stored blood products. RBCs are contaminated because of inadequate sterilization of collection bags. This contamination is caused by cryophilic gram negative organisms such as *Yersinia enterocolitica* and *Pseudomonas* species, and *Serratia*. Stored platelets are contaminated by *Staphylococcus*, *Klebsiella*, *Serratia*, and *Streptococcus* species.

Bacterial contamination may be difficult to prevent because of difficulty in screening and detection of contaminated units. Use of automated liquid media culture systems is now being supported (8) and has become mandatory in Netherlands and in some centers in the US. The system may not only save lives, but also prolong storage time of platelets. At times, gamma irradiation is used for decontamination of stored platelets although this can reduce platelet recovery and survival after transfusion and lead to more transfusion requirements. If contamination reaction is suspected, transfusion should be stopped (9,10). In cases of severe inflammatory response, empiric use of intravenous antibiotics may be a reasonable approach.

Other Infectious Disease Complications

Human immunodeficiency virus: The risk of HIV transmission through blood transfusion has dropped dramatically with the advent of new screening methods. The donor blood is now being checked for p24 antigen (11). The risk of transmission is approximately 1 in 1,900,000.

Hepatitis: The risk of transmission of hepatitis C virus used to be very high (1 in 200) with even use of volunteer repeat donors. Introduction of hepatitis C

virus antibody testing caused a further reduction. With the development of nucleic acid testing, the infectious window period dropped significantly and the risk of transmission is now as low as 1 in 1,600,000 (12,13). The major morbidity of hepatitis C infections is the chronic carrier state and cirrhosis.

Risk of hepatitis A transmission is estimated to be 1 in 1,000,000. In contrast to other types of hepatitis, it does not have the chronic carrier state.

Despite great success in lowering the transmission rate for hepatitis C, A, and HIV, hepatitis B still has a high rate of transmission which may vary from 1 in 50,000 to 1 in 150,000 in the western hemisphere (14).

Cytomegalovirus: Transmission of cytomegalovirus (CMV) can be a potential problem in patients with a compromised immune state such as ones with leukemia, lymphoma, transplant, and chemotherapy recipients. CMV-seropositive donors could potentially infect sero-negative recipients. The risk of transmission can be significantly reduced by transfusion of blood from a CMV-negative donor to a CMV-negative transplant recipient. It was previously thought that depletion of transfused blood from white cells using polymer gel filter could eliminate the risk of transfusion. However, new studies conclude that leukoreduced blood products are not considered totally CMV safe (15). New guidelines recommended transfusion of seronegative or leukoreduced blood products to all transplant patients who are CMV-negative and to chemotherapy patients who are likely to develop neutropenia.

Yersinia enterocolitica: This is a rare febrile reaction involving bacterial contamination of red blood cells with a frequency of one per million red cell transfusions. Reactions occur an hour or more after transfusion. The donor may have had a recent gastrointestinal illness caused by *Yersinia*, an anaerobic gram-negative bacillus that can cause diarrhea and abdominal pain. At the time of donation, the donor may be asymptomatic or mildly symptomatic with bacteremia. The bacteria could still grow and replicate at the temperatures blood is stored. If suspected, broad-spectrum antibiotics should be considered until culture results have excluded the cause. Complications of severe bacteremic states are endocarditis, meningitis, and splenic abscess. Mortality could be as high as 60% (16- 18).

West Nile Virus: The agent of transmission is a flavivirus which spreads the disease from birds to humans by mosquito bite. The virus has caused epidemics of meningitis and encephalitis in some of the eastern states. The disease can also be transferred through blood transfusion. Nucleic acid testing assays have been used in testing the donor blood in highly prevalent areas in which the rate of transmission has varied from 146 to 1233 per million donations (19).

NOSOCOMIAL INFECTIONS AND ORGAN FAILURE

Organ failure has been associated with transfusion. In a population of trauma patients who received blood early on, a linear correlation between early blood transfusion and subsequent development of multi organ failure was seen (20). It is speculated that pro-inflammatory mediators in the stored blood may be responsible for neutrophil activation that is involved in genesis of multiple organ failure. Blood by itself is also considered to be an immunosuppressant.

In a recent multivariate analysis, transfusion in the intensive care unit was independently associated with an increased risk for ventilator-associated pneumonia in critically ill patients on mechanical ventilation. The effect revealed a positive dose-response relationship; i.e. the more units of blood being transfused, the higher the probability of acquiring ventilator-associated pneumonia (21). In another large retrospective study, transfusion of blood had a dose-response relationship with the rate of

nosocomial infection in the intensive care unit. The patients who had transfusions were six times more likely to develop nosocomial infections compared to the non-transfused group. Each unit of blood increased the odds of development of nosocomial pneumonia by 1.5 (22).

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