

TRANSFUSION MEDICINE

Immediate Transfusion Reactions

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Immediate transfusion reactions were characterized in recipients of 15,990 RBCs, 18,013 platelets, 409 single donor platelets, 3,451 FFP and 1,507 units of cryoprecipitate. The overall incidence of immediate reactions was 0.2%. Allergic reactions occurred in 40 patients, febrile non-hemolytic in 36 patients, bacterial contamination in 2 patients, circulatory overload in 3 patients and mechanical hemolysis in one patient. Three

patients had nonspecific reactions. The incidence of immediate transfusion reactions was low when compared with similar studies. Possible causes are under-reporting transfusion reactions and the use of leukoreduced components.

Key words: Red blood cells transfusion, Platelets transfusion, Fresh frozen plasma transfusion, Cryoprecipitate transfusion, Transfusion reactions

Most transfusions provide the expected benefits of safe and effective replacement of blood components. However, blood transfusions can lead to an adverse outcome. These adverse effects of blood transfusion may occur as frequent as 10% of transfusion recipients (1-8). Rarely, an adverse reaction to transfusion can be fatal (9). Because many of the adverse effects associated with transfusion are not preventable, transfusion should be performed after careful analysis of its risks and benefits. Only when the benefits clearly outweigh the risks should a patient be transfused (10-12).

Transfusion reactions may be classified as immediate, when they occur during or within 24 hours of the completion of a transfusion and delayed. The severity of these reactions varies, but the majority of life-threatening reactions occur early in the course of transfusion. Therefore, all patients should be carefully monitored during transfusion and any adverse sign or symptom should be promptly investigated. Many serious adverse reactions to transfusion, particularly disease transmission, are delayed for weeks or years. Adverse reactions to transfusion also can be arbitrarily divided into immunologically mediated and non immunologically mediated. Although this distinction is artificial, it is useful for recalling the broad scope of potential adverse outcomes.

In this article we describe the immediate transfusion reactions in patients receiving RBC, platelets, fresh frozen plasma (FFP) and cryoprecipitate provided by the Transfusion Service of Puerto Rico Medical Services Administration (ASEM). The medical and laboratory assessment as well as the management of these reactions are also discussed.

Materials and Methods

Blood components. The Transfusion Service from ASEM provides components to the University Hospital, University Pediatric Hospital, Municipal Hospital of San Juan, Emergency Room of ASEM and Trauma Center. The Transfusion Service dispenses all blood components transfused to the patients of these hospitals. The blood components are purchased from the American Red Cross, Puerto Rico Chapter, and occasionally from the Servicios Mutuos Blood Bank. The Transfusion Service follows the standards of the American Association of Blood Banks and the regulations of the Food and Drugs Administration.

Transfusion reaction definition. Transfusion reactions are defined by professional standards (6,13) and described in the Blood Components Administration Procedure Manual. An adverse reaction is suspected and reported when the patient experienced any sign and symptom that can be related to transfusion, such as fever, chills, hives, pruritus, generalized malaise, dyspnea, nausea, vomits, diarrhea, abdominal pain, tachypnea, tachycardia, hypotension, bronchospasm and others. Fever was defined as $\geq 1^\circ\text{C}$ above basal temperature. At the time of a transfusion reaction, work up included completion of a transfusion reaction report that documented the patient's vital signs and symptoms, along with other pertinent

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information such as diagnosis, component type and amount transfused, history of previous reactions and premedication. Post transfusion blood and urine samples (if needed) along with the transfused unit bag were sent to the transfusion service for analysis. The laboratory investigation included a review of clerical records, examination of the pre transfusion and post transfusion serum for changes in color indicative of hemolysis, and direct antiglobulin test. Bacterial contamination of the unit was evaluated by Gram stain and by culturing the returned blood component bag, when the clinical evaluation is suggestive of bacterial contamination or when there is an increase of temperature $\geq 2^{\circ}\text{C}$ (14).

The pathology resident on call evaluated immediately the transfusion reaction and presented the case to the Transfusion Service physician, who reviewed each transfusion reaction report and the results of evaluation. Transfusion reactions were categorized as febrile, nonhemolytic, when the patient had a temperature elevation of at least 1°C during or immediately after the transfusion, and when other causes of fever are ruled out, such as transfusion-related acute lung injury (TRALI), bacterial contamination or immune hemolysis. We searched for other medical causes, such as suspected infection, for every case of fever associated with transfusion; the presence of any such condition excluded the patient in question of having a febrile reaction.

Hemolysis was diagnosed by the positive post transfusion direct antiglobulin test (positive in immune hemolysis) and by visual inspection of post transfusion plasma. The clerical revision and the ABO typing and crossmatch was performed in these cases. Bacterial contamination was diagnosed by positive culture of the unit and the patient with the same bacterial agent. If hives or urticaria were the major features of the reaction and no laboratory abnormalities were found, the reaction was labeled as allergic. When the symptomatology was more severe, with low respiratory tract reaction, hypotension and others, the reaction was labeled as anaphylactic. Reactions caused by the physical properties of the blood component (e.g., volume overload) were also reported to the Transfusion Service. When the reaction presented with signs or symptoms not meeting the criteria for the described transfusion reactions, they were listed as nonspecific. A reaction was recorded in more than one category if it had appropriate features; for example, we included a reaction with fever and urticaria as both febrile and allergic. Patients who experience two or more febrile episodes subsequently received leukoreduced components. Patients with two or more allergic reaction were premedicated with antihistaminics before transfusion. Patients with anaphylactic reactions received deglycerolized red blood cells.

Results

Incidence of reactions. The total number of blood components transfused in 1999 was 15,990 units of RBCs of which 3,767 were pediatric portions; 18,013 platelets; 409 single donor platelets; 3,451 units of fresh frozen plasma, of which 246 were pediatric portions and 1,507 units of cryoprecipitate. There were 85 transfusion reactions reported. The overall incidence of any reaction associated with any transfusion was 0.2 percent.

Allergic (urticarial) reactions. Allergic reactions were one of the most common adverse reaction (30 reactions). They occurred with any type of blood component with plasma: RBCs 15, platelets 9 and FFP 6. The reaction was developed by 17 adults (8 men and 9 women) and 13 children. Five patients had been premedicated with antihistaminics and one with antipyretic (acetaminophen).

The most common presenting symptom was urticarial rash in 30 patients, with pruritus in 11 patients. Other symptoms were angioedema in 2 patients, chills in 2 patients and generalized erythema in 2 patients. Twenty-one patients were treated with diphenhydramine (Benadryl®) and 13 patients also received steroids (Solucortef®).

Anaphylactoid or anaphylactic reactions. Anaphylactoid (severe allergic) reactions were observed in 8 patients. They occur with 4 transfusions of platelets, 3 transfusions of RBCs and one transfusion of plasma. Five patients were premedicated with antihistaminic (Benadryl®) and 3 with steroids (Solucortef®). The most common manifestation was respiratory difficulty (8 patients), laryngeal edema (1 patient) anxiety (1 patient) cyanosis (1 patient) nausea (3 patients), vomiting (1 patient), abdominal pain (1 patient) and diarrhea (1 patient). Six patients had urticarial rash and pruritus.

In addition to the allergic reaction, there were two cases that manifested also cardiovascular instability with hypotension, tachycardia and dyspnea. Both patients were premedicated with antihistaminic and steroids due to history of allergic reaction and both were treated with oxygen, antihistaminics and steroids.

Febrile non hemolytic reactions. Febrile reactions occurred in 36 patients, 17 men, 13 women and 6 children. The components transfused were 22 RBCs, 13 platelets and 1 FFP. Four patients were premedicated with antipyretics (acetaminophen) and four with antihistaminics (diphenhydramine).

Eighteen patients also presented chills and eleven patients presented chills without increased temperature of 1°C . Other symptoms were anxiety in two patients, tachycardia in three patients, dizziness in two patients, hypotension in two patients and loss of sphincter control

in one patient. Eight patients were treated with antipyretic (acetaminophen), 13 patients received steroids (Solucortef®), 10 received antihistaminic (Benadryl®), 2 received oxygen and one received meperidine (Demerol®).

Bacterial contamination. There were two cases of bacterial contamination. One patient developed a temperature increase of 3°C (from 36° to 38.8°C), accompanied by chills, rigors, and muscular aching after transfusion of one unit of RBCs. The patient was treated with antibiotics and steroids. Both the blood culture of the patient and culture of the unit were positive for *Escherichia coli*. The other patient developed a temperature increase of 2°C, (from 37 to 40.8°C), accompanied by chills after transfusion of random platelets. Both the blood culture of the patient and the culture of the unit were positive for *Staphylococcus epidermidis*.

Circulatory overload. Circulatory overload was diagnosed in three patients. The reaction presented as dyspnea, elevated blood pressure, cyanosis and tachycardia. The reaction presented in one child and two adults. The components transfused were RBC and FFP. The patients were treated with furosemide (Lasix®).

Mechanical hemolysis. In one patient, the diagnosis of nonimmune mechanical hemolysis was made. The patient received RBCs through an infusion pump, and experienced a change in the color of urine. Laboratory investigation demonstrates mechanical hemolysis due to a malfunctioning infusion pump.

Nonspecific reactions. Three patients presented with nonspecific reaction such as nausea, pain at infusion site and malaise.

Non-related to transfusion. Eleven reactions were considered not related to transfusion after careful evaluation. Examples included patients with rash or fever before transfusion, patients with BKP with respiratory distress and others.

Discussion

We have characterized the immediate transfusion reactions reported during 1999 at the Transfusion Service of the Puerto Rico Medical Center Administration and we have examined the management and prevention of these reactions. The incidence was 0.2 percent of units transfused.

Allergic reactions were noted with transfusion of platelets in 14 cases, with 7 transfusions of FFP and after transfusion of RBCs in 19 cases. The development of urticaria following transfusion is relatively common occurring in 1 to 2% of transfusion recipients (15). These reactions are thought to be mediated by antibodies to

soluble plasma proteins. Reactions to other allergens are frequent in the hospital. The differential diagnosis of an allergic transfusion reaction includes drugs reactions, allergy to tape or latex, underlying clinical conditions such as asthma and others (16).

When an allergic reaction appears, the transfusion should be stopped and IV access maintained. If there is dyspnea, oxygen should be administered. Mild allergic reactions respond to the administration of 50-100 mg IV diphenhydramine (Benadryl®). More severe reactions may require epinephrine. In mild cutaneous reactions, the transfusion can usually be resumed after treatment if there is improvement of symptoms. Thirteen of our patients were treated with steroids, although the efficacy has not been proven.

Premedication with an antihistaminic, such as diphenhydramine 25-50 mg, administered orally or IV may prevent mild allergic reactions. Seven patients were premedicated with antihistaminics and five with steroids. Steroids such as methylprednisolone (125 mg) may help patients who manifest repeated allergic reactions, although the efficacy of steroids has not been proven. Care should be taken when administering steroid to patients who require multiple transfusions because adrenal suppression may occur. Patients who have repeated or significant allergic reactions may benefit from the concentration of cellular blood components through the removal of the majority of plasma.

Febrile nonhemolytic transfusion reactions were found after 22 RBCs transfusions, 13 platelets transfusions and 1 FFP transfusion. Four patients were premedicated with antipyretics (acetaminophen) and four with antihistaminics (Benadryl®). A febrile transfusion reaction is defined as a rise in temperature of 1°C or greater, associated with transfusion and without any other explanation. The required elevation of 1°C is arbitrary, since the same events might cause temperature increments of 0.5° or 2°C without altering the physiologic significance (3,6,17). Fever may be accompanied by chills, cold or rigors. Secondary symptoms include headache, nausea, vomiting. Symptoms usually occur during the transfusion but may be delayed up to several hours after completion of the transfusion. The reaction is attributed to antibodies directed against transfused leukocytes and platelets (10).

Febrile nonhemolytic reactions are not life threatening, but prompt clinical evaluation is important to exclude other causes of fever. The differential diagnoses of febrile nonhemolytic reactions include hemolytic reactions, bacterial contamination, transfusion-related acute lung injury and disease or treatment-related fevers. In some patients, it may be impossible to distinguish between a febrile transfusion reaction and disease-related fever. In

general, when fever accompanies transfusion, a transfusion reaction should be ruled-out (18).

It is very important to promptly and properly investigate febrile reactions associated with the administration of a blood component, since fever can be the first symptom of an acute hemolytic transfusion reaction or may be associated with the infusion of a contaminated unit. Also TRALI presents with fever (19). At least, a clerical check, pre and post transfusion direct antiglobulin test and visual evaluation of serum for hemolysis should be performed (6). If bacterial contamination is suspected, a bacteriologic smear and appropriate cultures can be ordered. A properly identified post transfusion sample of blood obtained from the recipient, a compatibility slip and a description of the clinical transfusion reaction should be sent to the Transfusion Service in order to conduct the appropriate work-up (20).

Thus, in the event of a febrile reaction, hemolysis, TRALI and bacterial contamination must be ruled out and the patient should be treated. Antipyretics such as acetaminophen can be administered. However, antipyretics are not necessarily required, as the fever of nonhemolytic transfusion reactions is self-limited and usually resolves in 2-3 hours. Aspirin containing medications should be avoided because of the effect on platelet function. Diphenhydramine is commonly administered in this setting, but probably has no effect in the course of febrile reactions. Patients with severe shaking chills can be treated with meperidine (21). The anxiety occurring during a febrile reaction should not be ignored, and the patient should be reassured.

There is a controversy as to whether the transfusion can be restarted after a febrile reaction has been diagnosed and the patient has been treated. The principal argument in favor of restarting the transfusion is the reduction of donor exposures. Arguments against restarting the transfusion include the possibility that the patient may have a continued febrile reaction to the unit, and, if a hemolytic reaction or bacterial contamination has not been definitely excluded, a severe reaction may ensue. The decision of restart the transfusion should be driven by the clinical condition of the patient, the results of transfusion reaction testing and the particular policy of the hospital (22-23).

Premedication with antipyretics is often used to prevent febrile reactions. However, the efficacy has not been established. Acetaminophen in commonly used doses has few adverse effects; however, it is not generally recommended for patients who have not had previous febrile reactions. If a patient has had two or more febrile reactions, premedication may be indicated. It is unlikely that acetaminophen will mask serious reactions, such as

immune hemolysis or bacterial contamination. The routine uses of other premedication, such as diphenhydramine or steroids play no role in preventing febrile reactions (3,6).

As noted above, febrile transfusion reactions have been associated with acquired antibodies to leukocyte antigens in the transfused unit, particularly in multitransfused patients or multiparous women. It is generally accepted practice to use leukoreduction to prevent recurrent febrile responses in patients who have experienced two well-documented febrile reactions (24-31).

TRALI is a clinical diagnosis of exclusion, characterized by acute respiratory distress and bilaterally symmetrical pulmonary edema with hypoxemia developing within 2-8 hours after transfusion (32). In our cases, there is no TRALI identified; however, it may be severely under-reported due to failure to diagnose these reactions (33). The typical clinical presentation is one of respiratory distress, hypoxemia and hypotension in the immediate post-transfusion period, usually within 1 to 2 hours after transfusion. Fever and acute bilateral pulmonary edema also are described. The pathogenesis is related, in the majority of cases, to antibodies in donor serum reacting against recipient granulocyte antigens (34). The appropriate therapy is supportive with attention to adequate respiratory support. Most patients recover.

There were two cases of bacterial contamination, one after transfusion of RBCs and the other with platelets. Bacterial contamination is one of the earliest recognized complications of stored blood. It accounted for 29 (16%) of transfusion fatalities reported to the FDA between 1986 a 1991 (35). The clinical presentation of a transfusion reaction caused by bacterially contaminated blood components is usually dramatic. The onset of symptoms in most cases is during transfusion or shortly after it; fever, chills, hypotension, nausea and vomiting are the most common reported symptoms. Dyspnea and diarrhea may also occur. High fever and hypotension during or shortly after transfusion are particular clues that a contaminated unit may have been transfused. The clinical complications of bacterial contamination are significant, including shock, renal failure, DIC and death. The mortality rate is high and depends on the type of component transfused, the identity and amount of the causative organism and the clinical condition of the patient. The implicated units are most commonly platelets or RBCs. The organisms involved depend on the type and storage of blood component (36-42). *Yersinia enterocolitica* and *Pseudomonas* species are most commonly found in contaminated RBCs because their ability to grow at low temperatures. Both gram-positive such as *Staphylococcus* and *Streptococcus*, and gram-negative rods, such as *Salmonella*, *Escherichia* and *Serratia* have been reported in platelet concentrates (43-44)

Bacteria are believed to originate with the donor, either from the venipuncture site or from unsuspected bacteraemia. Bacterial contamination is more likely in components stored at room temperature than in refrigerated components. Organisms that multiply in refrigerated components are often gram negative. Gram-positive organisms are more often seen at room temperature. Strict adherence to phlebotomy protocol and scrupulous attention to sterile techniques during component preparation and storage should minimize contamination arising from sources outside the donor (45-47).

The differential diagnosis includes hemolytic reactions, febrile reactions, TRALI and sepsis unrelated to blood transfusion. The diagnosis is established through culture of the implicated unit and the patient's blood, bacteriological stains of the unit, endotoxin testing or DNA-based microbiological methods (6).

Prevention of bacterial contamination includes careful selection of blood donors and adequate procedure of phlebotomy and component preparation. Measures that have been proposed include extension of donor screening (48-53), improved skin disinfections (6, 54-55), limitation of storage time (47), and prestorage leukocyte reduction (56). Eventually, the use of detection systems may allow units to be monitored for contamination at the time of issue. Approaches include Grams stain, chemiluminescence probes, automated culture and determination of glucose consumption. There is not consensus on which of these techniques, if any, should be used (37).

Circulatory overload was identified in two patients, one child and one adult, after transfusion of RBCs and FFP. Transfusion related circulatory overload is a fairly common and preventable transfusion reaction. It presents as congestive heart failure during or immediately after transfusion with dyspnea, orthopnea, cyanosis, tachycardia, and systolic hypertension. Symptoms usually subside if the transfusion is stopped and the patient is placed in a sitting position and given oxygen and diuretics to remove fluid. If symptoms persist, a phlebotomy may be necessary (57-60). To avoid hypovolemia, blood components should not be infused at a rate faster than 2-4 ml/kg/hour. Slower rates are needed for patients at risk of fluid overload, such as patients with chronic anemia who have an expanded plasma volume or patients with compromised cardiac or pulmonary function. In those situations, aliquots from a single unit of blood can be transfused slowly over time (38). When autologous blood is available, conservative transfusion practices should be followed. Although controversial, some authorities favor the use of the same criteria for the transfusion of both autologous and allogeneic blood (61-62). Careful attention should be paid to the patient's fluid balance prior to

transfusion of any blood component, especially in elderly or infant populations.

Mechanical hemolysis was identified in one patient, after transfusion of RBCs through an infusion pump. Lysis of red cells can occur as a result of storage, handling or transfusion conditions. Patients who received hemolyzed red cells may tolerate them well, although transient hemodynamic, pulmonary and renal impairment may occur. Mechanical hemolysis may be caused by the use of roller pumps, pressure infusion pumps, pressure cuffs or small bore needles. The clinical signs are usually hemoglobinemia and hemoglobinuria (6). Finding lysis of red cells in the transfused unit and excluding others causes, such as immune hemolysis, establishes the diagnosis. Non immune hemolysis is prevented by proper handling, storage and transfusion practices. All staff should be trained in the proper use of equipment, intravenous solutions and drugs used during the administration of blood and blood components. Equipment should be properly maintained (63-64).

Conclusion

We report the incidence of different types of immediate transfusion reactions that were evaluated by our Transfusion Service at the Puerto Rico Medical Services Administration during 1999. The incidence of these reactions is low when compared with similar studies in the literature. The reasons for the lower incidence has not been established, but this may be due to under reporting of these events of that important amount of blood components are currently leukoreduced, decreasing the number of reactions related to leukocytes is low, as compared with reported in the literature; the cause has not been established, but may be that transfusion reactions are underreported or that an important amount of components transfused are leukoreduced, decreasing the number of reactions induced by leukocytes.

Resumen

Se caracterizaron las reacciones a transfusión inmediatas de recipientes de 15,990 unidades de células rojas, 18,013 unidades de plaquetas, 409 unidades de aféresis de plaquetas, 3,451 unidades de plasma fresco congelado y 1,507 unidades de crioprecipitado. La incidencia de reacciones a transfusión inmediatas fue de 0.2%. Se diagnosticaron 40 pacientes con reacciones alérgicas, 36 pacientes con reacciones febriles no hemolíticas, 2 pacientes con contaminación bacteriana, 3 pacientes con sobrecarga de volumen y un paciente con hemólisis mecánica. Tres pacientes presentaron reacciones no

específicas. La incidencia de reacciones a transfusión inmediatas fue baja cuando se compara con estudios similares. Posibles causas incluyen que no se estén reportando todas y la utilización de componentes leucorreducidos.

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