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Review Article

Indications and complications of blood transfusion

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ABSTRACT

Blood transfusion is a common procedure in the realm of medicine and surgery to treat hematological disorders such as iron and hemoglobin deficiency, during and after major surgical or invasive procedures, and in the event of trauma. However, this life saving procedure does not come without adverse complications and risks. In this review we will extensively discuss the indications of blood transfusion and the complications associated with blood transfusion. An extensive literature search was conducted in online databases such as PubMed, Google Scholar to include various publications such as narrative reviews, editorials and clinical practice guidelines on the indications of blood transfusion and its associated complications. After numerous large scale clinical trials and studies, the transfusion trigger for hemoglobin has been readjusted to a lower threshold thus preventing excessive transfusions and thereby limiting complications. There are a wide range of complications and adverse events associated with blood transfusions. Non-infectious transfusion reactions can contribute to significant morbidity and mortality and occur more commonly as compared to infectious transfusion reactions. Non-infectious reactions can be immune mediated and non-immune mediated and can also be subdivided based on their timing and occurrence after transfusion as acute occurring within 24 hours of transfusion and delayed as occurring 24 hours after transfusion. Further studies are warranted to create more precision on indications of blood transfusion especially for blood components such as platelets, fresh frozen plasma and cryoprecipitate are still undefined and need further trials to set cut-off limits to indicate transfusion.

Keywords: Indications, Blood, Transfusion, Complications

INTRODUCTION

Blood transfusion is a therapeutic process which replaces whole blood or certain components of blood products in the circulatory system intravenously in the event of a major blood loss due to injury or trauma, during a major surgery or in medical conditions with inadequate production of blood cells such as thalassemia or leukemia, or increased destruction of red blood cells.[1-3] Blood transfusions are an extremely common procedure among patients especially undergoing major surgery or hemorrhage. The Association for the advancement of blood and biotherapies, (formerly

known as the American association of blood banks) report the rates for annual blood transfusions globally are 85 million, 15-24 million red blood cells in the United States of America are whereas 2.5-3 million units of blood are transfused in the United Kingdom.[4-6]

According to the American red cross, there are different components of blood available for transfusion as required by the recipient, such as whole blood, red blood cells (RBC), fresh frozen plasma (FFP), platelets, cryoprecipitate.[7,8] RBC transfusion is carried out for three main purposes, namely, to improve circulatory status if there is volume depletion, to improve viscosity and to improve oxygen delivery to tissues.[9] Clinical practice guidelines for blood transfusion use the rationale of 'transfusion triggers' which are defined as the value of hemoglobin (Hb) below which a blood transfusion is indicated.[9] Previous guidelines mandated a Hb level equal to or less than 10 g/dl, or the 10/30 rule in which blood transfusion was carried out either, when the Hb level was ≥10 g/dl (100 g per l) and a hematocrit ≥30%.[7] However, after major advancements and clinical trials in transfusion medicine the 'transfusion trigger' has been readjusted as there has been conflicting evidence over selection of Hb as the sole and predominant factor for blood transfusion over the years.[10]

After conducting numerous clinical trials, guidelines on blood transfusion have been updated worldwide to include patient co-variables and other factors to ensure necessary and safe blood transfusions thereby minimizing excessive and unnecessary transfusions and preventing adverse effects and infections.[6,10] There have also been major debates surrounding the risks or complications and adverse events of blood transfusion in existing literature.[7] Despite careful selection by a donor and highly stringent testing for compatibility and infections, transfusions can lead to complications such as infections and even fatalities.[11,12] In this literature review, we will discuss the various indications of blood transfusion and their associated complications.

METHODS

A thorough search was conducted from electronic databases such as PubMed, Medline Embase, Google Scholar and Cochrane library. To avoid missing potential studies, a further manual search for papers was done through Google Scholar. Literature reviews, clinical practice guidelines and editorials were the publications that were included in our literature review. Blood transfusion guidelines specified for adults were mainly included in our review.

DISCUSSION

Indications for blood transfusion

Blood transfusions have become more restrictive based on updated clinical practice guidelines to avoid unnecessary transfusions and in effect prevent adverse events.[11] The best transfusion practices for individual blood components have evolved over the years and clinical practice guidelines have been updated after numerous clinical trials.

Red blood cell transfusion

As opposed to the previous practice of a liberal transfusion, the Association for the advancement of blood and biotherapies now recommends a restrictive approach and is only indicated if Hb is less than 7-8 g/dl (70-80 g per l) in hospitalized adult patients and children that are hemodynamically stable and critically ill patients with a target Hb maintenance at 7-9 g/dl.[6,13-15] A prominent multi-center study was conducted by Hébert et al where patients were divided into a restrictive transfusion group where transfusion is indicated if Hb <7 g/dl and a liberal transfusion group where transfusion is indicated at Hb <10 g/dl. Patients in the restrictive transfusion group had the same 30-day mortality rates as the liberal transfusion group.[16] Studies have also reported that major randomized controlled clinical trials have been conducted on restrictive RBC transfusion which have demonstrated a 54% decrease in units transfused and furthermore, a decrease in 30-day mortality rate has also been observed.[6,13] In addition, RBC transfusions should be carried out based on the patient's clinical presentation and conditions such as acute sickle cell crisis, acute blood loss greater than 1500 milliliters or 30% blood volume and symptoms of anemia such as fatigue, dizziness, palpitations, shortness of breath on minimal exertion.[7] There are special circumstances in which the threshold for RBC transfusion has been lowered to of ≥8 g/dl such as patients that maybe hemodynamically stable but suffering from cardiovascular disease, showing symptoms of impaired oxygen delivery to tissues such as chest pain, orthostatic hypotension refractory to fluid resuscitation and patients undergoing cardiac, orthopedic surgery.[6,9,13]

Platelet transfusion

Separate transfusions of platelet concentrates did not become common practice until the late 1970s.[4] Platelet transfusion is indicated when there is a risk of hemorrhage or active bleeding in case of a platelet deficiency or thrombocytopenia and platelets with functional defects.[7] Transfusions cane be carried out both prophylactically and therapeutically depending on the requirement and the patient's hematological status. According the guidelines by the National blood transfusion committee by the National health service prophylactic platelet transfusions are indicated when platelet levels $<10\times9^9$ l in reversible bone marrow failure or when levels are $10\text{-}20\times9^9$ l during sepsis or hemostatic disorders and prior to major surgeries and invasive procedures.[14] Platelet transfusions can be done therapeutically to treat bleeding in the event of major hemorrhage with platelet levels of $<50\times9^9$ l, when there is bleeding from a critical site such as the central nervous system and platelet levels are $<100\times9^9$ l.[14] There is still no

concrete transfusion trigger for platelet transfusion prophylactically, the optimal dosing for platelet transfusion. However, Goodnough et al reported that Rebulla and colleagues conducted clinical trials and reduced the platelet transfusion threshold for prophylactic platelet count transfusions in patients suffering from hematological cancers has been reduced from $<20\times9^9$ l to $<10\times9^9$ l which led to a significant reduction in platelet transfusions with little to no increase in bleeding.[4]

Fresh frozen plasma transfusion

Patients suffering from acute disseminated intravascular coagulation with abnormal bleeding and a deranged coagulation profile, especially in liver diseases should be transfused with FFP.[11,14] They are also indicated in cases of active bleeding, especially before a surgical procedure, reversal of anticoagulant effects such as warfarin, if the international normalized ratio is >1.6 and microvascular bleeding during a massive transfusion.[4,7,8,11] However, there is very limited evidence and studies on the efficacy of plasma transfusions for both therapeutic and prophylactic transfusion. Large scale studies have been given platelet transfusions with very insignificant changes in coagulation profiles and even in the absence of bleeding.[4] Thus further research is warranted on the efficacy and threshold of plasma transfusion.

Cryoprecipitate transfusion

Cryoprecipitate should be transfused in the event of massive hemorrhage to replace a glycoprotein complex called fibrinogen which is converted to fibrin which is primarily responsible for formation of blood clots and occluding bleeding from blood vessels when it is <than 1.5 g/liter or <2 g/liter in major obstetric bleeding.[11,17] Each unit of cryoprecipitate raises fibrinogen by 5 to 10 mg/dl with a target of maintaining a fibrinogen level of 100 mg/dl.[7] It is also transfused in patients with acquired hypofibrinogenemia. Similar to FFP, the threshold for cryoprecipitate is constantly changing, and thus further clinical trials should be conducted on the threshold and dose for cryoprecipitate.[4]

Complications

Although blood transfusions can be a lifesaving procedure, they carry their own risks and complications. Blood transfusions can cause infectious as well as non-infectious reactions and can be referred to as non-infectious adverse transfusion reactions and can contribute to significant morbidity and mortality.[18]

Non-infectious adverse transfusion reactions can be further subdivided into immune mediated and non-immune mediated. Non-infectious adverse reactions can be acute where they occur within minutes to hours or within 24 hours of the transfusion and delayed which occur after 24 hours of transfusion.[7,18]

Acute immune mediated

Acute hemolytic transfusion reactions

A mismatch between RBCs of donor cell and recipient lead to an immune reaction by the recipient's preformed antibodies towards the donor's red cell antigens causing a destruction of the transfused RBCs. Acute hemolytic transfusion reactions occur in 1 to 5 of 50,000 transfusions symptoms occur within minutes after the transfusion begins and range from fever with chills and rigors, nausea, vomiting oliguria, anuria, backpain, pain the chest and abdomen, hypotension, pain along the intravenous line. The common laboratory findings of this complication are hemoglobinemia, hemoglobinuria, unconjugated hyperbilirubinemia, increased lactate dehydrogenase, and decreased Hb.[7,18]

Febrile non-hemolytic transfusion reaction

A febrile non-hemolytic transfusion reaction is identified by a 1 degree Celsius (1.8-degree Fahrenheit) rise in body temperature above 37 degrees Celsius (98.6 degrees Fahrenheit) within 24 hours of a blood transfusion. A systemic inflammatory response involving cytokines and antibody mediated pyrogens cause symptoms of fever, chills and rigors. Febrile hemolytic transfusion reactions are more common with platelet transfusions and are associated with up to 35% platelet transfusions. The incidence of febrile hemolytic transfusion reactions can be reduced by leukoreduction which is the removal of white blood cells from donor blood.[7,18]

Urticaria

Urticarial reactions are a mild form of allergic reactions to blood transfusion characterized by itching or hives and occurring within seconds of the transfusion and may last for hours or even days before subsiding. The incidence of urticaria is 1-3% of transfusions urticarial reactions are cause by sensitization of the recipient to the donor's antigens.[7,18]

Anaphylaxis

An anaphylactic reaction is a more severe form an allergic reaction to a blood transfusion with severe symptoms of hypotension, bronchospasm, stridor, loss of consciousness, shock and gastrointestinal symptoms occur. The incidence of anaphylactic reactions during blood transfusions is 1:20,000 to 1:50,000.

The pathophysiology of an anaphylactic reaction is the recipient's pre-sensitization to the donor's plasma proteins such as immunoglobulin A being transfused to an immunoglobulin A deficient recipient with pre-formed antibodies to the immunoglobulin. Anti-human leukocyte antibodies and anticomplement antibodies are also associated with anaphylactic reactions.[7,18]

Transfusion related acute lung injury

Transfusion related acute lung injury (TRALI) is an impairment of pulmonary function and pulmonary edema that maybe be transient and is non-cardiogenic in nature. It occurs as an adverse reaction and occurs during or within 6 hours of blood transfusion resolving within 48-96 hours in 80% of patients undergoing transfusion, however it is associated with high morbidity and mortality. It is estimated to occur in 1 in every 5000 transfusions and is associated with all the components of blood i.e. whole blood, RBCs, platelets, FFP and cryoprecipitate. TRALI is purely a clinical diagnosis which can be supported by laboratory findings. Characteristic clinical and radiological features of transfusion related acute lung injury are, hypoxemia with PaO_2/FiO_2 of ≥300 or SpO_2 of <90% on room air, evidence of bilateral pulmonary edema on chest radiograph. Patients with this form of lung injury have no prior risk factors. The recipient's immune system is activated by Antineutrophil cytoplasmic antibodies or anti-human leukocyte antigen antibodies causing a massive pulmonary edema. Furthermore, activated neutrophils secrete proteolytic enzymes causing lung tissue damage.[7,18]

Acute non-immune mediated reactions

Transfusion related sepsis

Transfusion related sepsis, although rare is a severe and even fatal complication. The diagnostic features are at least one of the following: a fever ≥39°C (102°F) or rise of ≥2°C (3.5°F), tachycardia with >120 beats per minute, or an increase of >40 beats per minute, chills and rigors and a change in systolic blood pressure with a >30 mmHg rise or drop in systolic blood pressure within 90 min of transfusion. Renal failure and disseminated intravascular coagulation may also occur in severe cases.[18] Platelets are at a higher risk for bacterial contamination with 1-2% chances as compared to 0.4% of RBCs as platelets are stored at room temperature.[3,18] The causative organism can be isolated from the patient and the remainder of the blood bag. Bacterial contamination can occur in 65% of venipunctures during blood sample collection despite disinfectant use.[18] The most common bacterial pathogen from the donor's skin entering the blood collection unit is *Staphylococci*, whereas the most common bacterial pathogen collected from the bloodstream in transfusion related sepsis was *Yersinia*.[3]

Non-immune hemolysis

Red cell hemolytic reactions also known as pseudo hemolysis due to blood transfusion can also occur due to non-immunological reactions such as variations in temperature or mechanical causes. Improper temperature at storage, incorrect use of blood warmer, using a needle with small bore size of needle for transfusion, infusing RBCs through tube that was used to infuse a hypotonic solution are probable causes of non-immune hemolytic reactions.[18]

Transfusion associated circulatory overload (TACO)

Transfusion associated circulatory overload (TACO) is caused by a rapid transfusion of a blood volume that is beyond the capacity of the recipient's circulatory system. Patients with a compromised circulatory system are most susceptible such as patients with cardiopulmonary compromise, renal failure, patients with hypoalbuminemia, fluid overload and elderly or infant population. Although it is seen in <1% of patients undergoing transfusion, it is associated with a high morbidity and mortality. The signs and symptoms of TACO are breathing difficulties such as dyspnea, orthopnea, tachypnea, tachycardia, cyanosis, jugular venous distension, elevated central venous and pulmonary wedge pressure and pedal edema. A characteristic feature of TACO is hypertension associated with a wide pulse pressure. Chest radiographs may reveal cardiomegaly and pulmonary edema Brain natriuretic peptide will be elevated in TACO and can aid in facilitating a diagnosis. Blood transfusion should be carried out at slower rates and a lower volume to prevent this complication.[7,18]

Delayed immune mediated reactions

Delayed hemolytic transfusion reaction

Delayed hemolytic transfusion reactions occur due to reactivation of pre-formed antibodies against antigens of transfused RBCs. The incidence of these reactions is estimated to occur in 1 in 6000 transfused units. Although RBCs have been cross-matched and tested for compatibility, symptoms occur days or even weeks after transfusion. Patients with delayed hemolytic reactions will have unexplained anemia or no changes in Hb level even after blood transfusion. As destruction of RBCs occurs gradually as antibody formation occurs therefore treatment is not required. However, if the patient has low levels of Hb and is bleeding, RBCs with free of antigens will be needed.[18]

Transfusion associated immunomodulation

The suppression of the recipient's immune response by transfused allogenic blood is called transfusion associated immunomodulation. The downregulation of the immune response by transfused blood can cause post-operative infections, re-occurrence of cancers and even transfusion related multiple organ dysfunction syndrome. Common speculations for the mechanism of this adverse reaction is a complex interplay of immune deviation towards type 2 T-helper lymphocytes cytokine secretion of interleukin-4, interleukin-5, interleukin-10 with a reduced secretion of type 1 T-helper lymphocyte cytokines interleukin-2, interleukin-12 and interferon-g. Prestored leucofiltered blood can reduce the detrimental effects of transfusion associated immunomodulation.[18]

Transfusion associated graft versus host disease

Transfusion associated graft versus host disease (TA-GVHD) is a highly fatal complication with a 90% mortality rate caused by the donor's lymphocytes in which transfused T-lymphocytes cause an immunologic attack on the recipient's tissues and organs which is incapable of rejecting the immunocompetent transfused cells. Patient groups that are most susceptible to this transfusion reaction are the immunocompromised, the immunocompetent and patients who receive transfusion from blood related donors with a shared human leukocyte antigen haplotype. The transfusion reaction is characterized by a maculopapular rash progressing to hemorrhagic bullae, fever, deranged liver function tests, enterocolitis, watery diarrhea, and pancytopenia one to six weeks after transfusion. Some common risk factors include history of chemotherapeutic agents and cytotoxic drugs, Hodgkin's disease, stem cell transplant and pairs of recipient and donors from homogenous populations.[3,18]

Post transfusion purpura

Post transfusion purpura (PTP) is a relatively rare yet fatal complication occurring predominantly in multi-gravida female patients. The reaction occurs between 1- and 24-days post transfusion with a mean of 9 days. PTP is characterized by a purpuric rash and thrombocytopenia with platelet levels of <10,000/µl causing bleeding from mucous membranes, gastrointestinal and urinary tract however, intracranial hemorrhage is the primary cause of mortality. PTP is commonly associated with whole blood, RBCs, platelets and plasma. The reaction is caused by antibodies towards platelets antigens and human leucocyte antigens.[3,18]

Delayed non-immune mediated

Iron overload

Patients receiving chronic transfusions for hematological diseases such as sickle cell anemia, thalassemia, chronic anemia are at the greatest risk for iron overload. As the red cells are destroyed, the excess iron is stored as hemosiderin and ferritin. Transferrin saturation occurs after the transfusion of 10-15 units of RBCs and iron is stored in the reticuloendothelial system and organs such as liver, spleen, heart and endocrine organs thereby causing failure of organs such as the liver, heart, diabetes and hypothyroidism.[18]

Transfusion transmitted infections

Some of the most commonly transmitted infections through blood transfusions are hepatitis B, hepatitis C, human immunodeficiency virus, whereas some rarely transmitted infections are malaria, Creutzfeldt-Jakob disease.

The incidence of transfusion related infections has significantly decreased because of the meticulous and advanced screening and testing processes. The risk of acquiring an infection from a transfusion has decreased 10,000 fold since the 1980s.[3,7]

CONCLUSION

Blood transfusion is a lifesaving procedure that is being practiced in clinical medicine since many decades as therapeutic and prophylactic management in various hematological diseases, in major surgeries and hemorrhage. Although transfusion medicine has evolved from a liberal to a more restrictive transfusion strategy, there is still a wide gap in the knowledge, and practice of blood transfusions due to undefined thresholds for various blood components in clinical practice guidelines. Furthermore, blood transfusions are associated with high risks and complications. Therefore, further clinical trials and large-scale studies need to be conducted to define thresholds for components that still do not have transfusion triggers creating more refinement in transfusion medicine with lesser risks and complications.

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