CHAPTER

100

Blood Component Therapy

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ABSTRACT

Blood component therapy has advanced over the past few decades. Its application has found roots in almost all specialties. So a doctor (whichever specialty he practices) should know about the basic principles of blood component therapy. He should know the various indications in his specialty, and should be familiar with the type and dose of the components which he should order for these various indications.

Red cell transfusions are given to increase the hemoglobin level in patients with anemia. Whole blood transfusion is restricted to patients who need an additional volume replacement e.g. an adult who has bled acutely and massively. Current practice is restrictive red cell transfusion policy. Transfusion is not indicated if the HB level is more than 10 g/dL and usually indicated if the HB level is less than 7 g/dL. The only important exception to this rule is ongoing symptomatic myocardial ischemia where the threshold is 10 g/dL.

Plasma components which are commonly ordered are FFP and cryoprecipitate. They contain all the requisite plasma coagulation factors in a slightly reduced quantity than plasma. Cryoprecipitate contains Factor VIII, Factor XIII, fibrinogen, fibronectin and VWF. FFP is used to replace coagulation factors in case of major bleeding associated with warfarin anticoagulation and or with vitamin K deficiency. It is also used for treating bleeding episodes associated with liver disease, DIC, as a component in massive transfusion protocols and as a source of factor replacement in rare inherited coagulation disorders. Cryoprecipitate is indicated in congenital and acquired deficiency of fibrinogen and factor XIII and in uremic bleeding.

For platelet transfusions, platelets are collected either by isolation from a unit of donated blood (Random donor platelet- RDP) or by apheresis from a donor in blood bank (Single donor platelets-SDP). SDP is always better than RDP because the recipient is exposed only to one donor and one unit of SDP will yield platelet number equal to platelet number in six units of RDP. Platelet transfusion is given 1) Therapeutically (to treat active bleeding or in preparation for an invasive procedure that would cause bleeding) or 2) prophylactically (to prevent spontaneous bleeding when the platelet count is low). Platelets are stored in room temperature and transfused quickly in patients who are bleeding to keep the platelet count above 50,000/microL in most situations and above 100,000 in case of nervous system bleeding. Guidelines are available for preparation of an invasive procedure. Prophylactic platelet transfusions are usually given when the platelet count is less than 10,000/microL. In ITP and Dengue fever with thrombocytopenia, platelets are given only if there is bleeding.

There is renewed interest in granulocytic transfusion after overcoming the difficulties in collecting adequate amount of viable functional granulocytes. Granulocyte transfusion is indicated when the absolute neutrophil count (ANC) is less than 500/microL, evidence of bacterial or fungal infections and unresponsiveness to antimicrobial treatment. Indications are neutropenia from chemotherapy or transplantation, aplastic anemia, chronic granulomatous disease and neonatal sepsis.

The most important and fatal complication of component therapy is transfusion associated GVHD (ta-GVHD). Complications can be reduced by leuko reduction; irradiation and giving ABO and HLA matched components.

INTRODUCTION

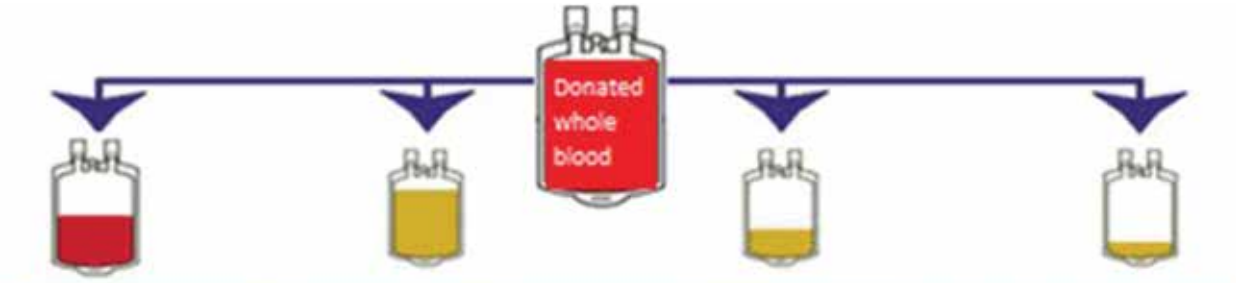
Blood components used in clinical practice are whole blood, red blood cells, plasma components, platelets, lymphocytes and granulocytes which are derived from whole blood or platelet rich plasma. (Figure 1) These components are collected from normal donors by phlebotomy or hemapheresis using the technique of differential centrifugation. Blood components should be distinguished from plasma derivatives which are fractionated from large volumes of (thousands of litres) plasma in large industrial units e.g. for manufacturing albumin, intravenous gamma globulin, Factor VIII etc.

Major blood components which are going to be discussed in this chapter are red cells, platelets concentrates, fresh frozen plasma and cryoprecipitate.

RED CELL TRANSFUSIONS

Red cell transfusions are given to increase the hemoglobin level in patients with anemia or to replace losses after acute bleeding episodes.

Whole blood should be considered as the choice only when treating an adult who has bled acutely and massively, where volume replacement is necessary. Patients with chronic anemia should be transfused with RBCs (Packed RBCS – PRBC) as volume replacement is not required. With the current use of CPD- Adenine as the anticoagulant preservative (AP) solution and use of the new generation additive solutions, the red cells can be stored for 35 – 42 days.



Packed Red Blood Cells (PRBC)	Plasma (FFP)	Platelet Concentrates (RDP)	Cryoprecipitate
Indications: To increase the amount of red blood cells after trauma, surgery or to treat anaemia	To correct a deficiency in coagulation factors or to treat shock due to plasma loss from burns or massive bleeding	To treat or prevent bleeding due to low platelet levels. To correct functional platenet problems	To treat fibrinogen and FVIII deficiencies
	PERIOD THE COMPONENT CAN BE STORED		
42 days in the refrigerator or 10 years in the freezer	1 year in the freezer	5 days at room temperature	1 year in the freezer

Fig. 1: The Components of Human Blood

Indications – Since anemia is associated with adverse clinical outcomes, red cell transfusion is indicated in conditions of anemia. The current consensus is a restrictive policy for transfusion. Red cell transfusion is not indicated if HB is more than 10 g/dL. It is generally indicated if the value is less than 7 g/dL. It is found that in various clinical trials, restrictive policy is safe, improves clinical outcomes and reduces unnecessary transfusion even in ICU setting.

The exceptions to this rule are

1. Patients with symptomatic myocardial ischemia with HB < 10g/dL should be transfused to improve hemodynamic instability.
2. In patients with acute coronary syndrome, an individualistic approach should be followed. In general it is desirable to have the HB equal to or more than 10g/dL.
3. In patients requiring massive transfusion (e.g. trauma or ongoing bleeding) a strict HB threshold may not be possible.

The volume of one unit of RBCs with citrate-phosphate-dextrose adenine (CPD-A1) anticoagulant is between 225 – 350 ml. Several complications of RBC transfusion seem to be due to contamination with leukocytes. The complications are febrile non hemolytic transfusion reactions, HLA alloimmunization, post-operative infection and cardiac reperfusion injury. These complications can be reduced by leukocyte reduction filters. Transfusion associated graft versus host disease which is a fatal complication, cannot be reliably prevented by leuko reduction and requires irradiation of the blood products.

PLASMA COMPONENTS

1. FFP - The plasma that is separated and frozen at -18°C to -30°C within 8 hours of collection is called FFP.
2. PF24 – Plasma that is separated and frozen at -18°C - -30°C within 24 hours of collection is called PF 24.

   These can be stored for one year. Both these components contain all the requisite plasma coagulation factors in a slightly reduced quantity than plasma. As the clotting factors are not in a concentrate form, FFP should not be used as a source of specific clotting factors.
3. Thawed plasma – Thawed plasma is plasma that was frozen (FFP & PF24), thawed and kept at refrigerator temperature for up to 5 days.
4. Liquid plasma – Liquid plasma is plasma that has never been frozen.
5. Solvent/Detergent plasma (S/D plasma) – S/D plasma is plasma treated with viral inactivating agents prior to freezing.
6. Plasma cryoprecipitate reduced - Plasma cryoprecipitate reduced is plasma from which cryoprecipitate has been removed. This is also called cryo-poor plasma.

FRESH FROZEN PLASMA

This can be taken as a prototype of many of the plasma components and will be discussed in detail. This can be prepared from single units of whole blood or from plasma collected by apheresis techniques. Standard FFP unit collected from single unit has a volume of approximately 200 – 250 mL.

Indications

1. Coagulation factor replacement in the management of major bleeding associated with warfarin anticoagulation and or Vitamin K deficiency.
2. To treat a deficiency of multiple coagulation factors e.g. liver disease Disseminated intravascular coagulation.

3. As a component of massive transfusion protocols.
4. FFP is also used as source of factor replacements for rare inherited coagulation factor disorders.

Warfarin associated intracranial hemorrhage is a medical emergency with an extremely high morbidity and mortality. After stopping the anti-coagulant, the ideal treatment is Vitamin K 10mg given by slow intravenous infusion not faster than 1mg/min to minimize anaphylactic shock. The effect of Vitamin K is delayed and takes about 12 to 24 hours. So for immediate action, 4 units of FFP should be given along with vitamin K, if better options like PCC (Prothrombin complex concentrates) are not readily available for a rapid action. The same principle is used for treating other serious bleeding episodes associated with supra therapeutic range of INR. Rare inherited deficiencies of factors XIII, X, VII, V and II are treated with FFP when they develop bleeding and when these rare factor concentrates are not easily available. FFP is used as a source of factor V in severe cases of DIC with persistent bleeding. The persistent bleeding in this situation is thought to be due to a factor V deficiency rather than a global decrease in coagulation factors. So it is also given for congenital Factor V deficiency. PF 24 should not be given under these circumstances as it contains reduced levels of factor V.

FFP may be used in the unlikely circumstance when a specific factor concentrate or recombinant product is not available for managing bleeding in a patient with a coagulation factor deficiency (e.g. Factor VIII, IX, and XIII). This circumstance is very common in India.

Liver disease leads to a form of "rebalanced" hemostasis, in which diminished hepatic function leads to both procoagulant and anticoagulant effects. It is now clearly established that in CLD there is a decrease in the anticoagulant factors as Protein C and Protein S together with a decrease in Vitamin K dependant clotting factors. The decreased Protein C and Protein S will lead to a prothrombotic state in CLD. If this prothrombotic state is dominant, patients with CLD and prolonged INR may not bleed but may actually go on for thrombosis: e.g. Portal vein thrombosis and lower extremity DVT. So an increased INR may not truly indicate the actual balance of bleeding and the prothrombotic state in CLD. For these reasons FFP is now given only when there is bleeding associated with prolonged INR in CLD. There is also no indication for FFP for treating bleeding or as prophylaxis for invasive procedures in patients with INR<2.

There is also little evidence to support the practice of administering FFP to correct the INR prior to performing an invasive procedure. Solvent detergent treatment of FFP (S/D plasma) is effective for use in liver transplantation.

Dose and infusion rate

The usual dose of plasma is approximately 10-15 mL/kg (i.e. approximately three to five units) in most adults. But this dose (750-1250 mL) represents a significant volume challenge. The infusion rate is:

- For healthy adult 2-3 mL/kg/hour (i.e. approximately one unit in 1.5 hours).
- For patients with volume overload or heart failure 1mL/kg/hour (approximately one unit in 4 hours).
- For patients undergoing plasmapheresis, 60mL/minute; this can be increased to 100mL/minute if the patient tolerates well.

The potential risks of plasma exchange include infection, volume overload, febrile and allergic reaction, anaphylactic reaction, TRALI (Transfusion-related acute lung injury).

Cryoprecipitate: (Cryoprecipitated Anti Hemophilic Factor – AHG)

This is the precipitate that forms when FFP is thawed at 4°C. This precipitate (cryo) is separated from the thawed plasma by centrifugation. Cryo is a concentrated preparation that contains all of the factor VIII, Fibrinogen, Fibronectin, factor XIII and vonWillebrand factor (VWF) from the FFP. It is reduced from an initial volume of 250mL to a final volume of 10mL. The remaining portion can be refrozen and used as Plasma Cryoprecipitate Reduced (or Cryo-Poor Plasma). Cryo cannot be made from PF24 because the level of factor VIII is very low. Cryo contains approximately 200mg of fibrinogen and 100 units of Factor VIII per unit. It carries an equivalent infectious risk as a unit of plasma.

Indications

1. Congenital and acquired deficiency of Fibrinogen e.g. CLD is an acquired deficiency.
2. Congenital and acquired deficiencies of Factor XIII.
3. Rarely it is used in uremic bleeding that does not respond to other measures.

PLATELET TRANSFUSION

Platelets are collected either by isolation from a unit of donated blood or by apheresis from a donor in the blood bank.

1. Pooled platelets – One unit of platelet can be isolated from every unit of donated blood by centrifuging the blood within the closed collection system to separate the platelets from the red cells (RBC). The average platelet yield from one unit is 7×10^{10} platelets. This number is inadequate to increase the platelet count in an adult recipient. Four to six units are pooled to allow transfusion of 3 to 4×10^{11} platelets per transfusion. These are called random donor pooled platelets (RDP). The lower cost and the ease of collection and processing are the advantages of RDP. The major disadvantage is the recipient exposure to multiple donors in a single transfusion and issues regarding bacterial testing.
2. Apheresis (single donor) platelets SDP – In this method of collection, platelets are collected from volunteer donors in the blood bank in a one to

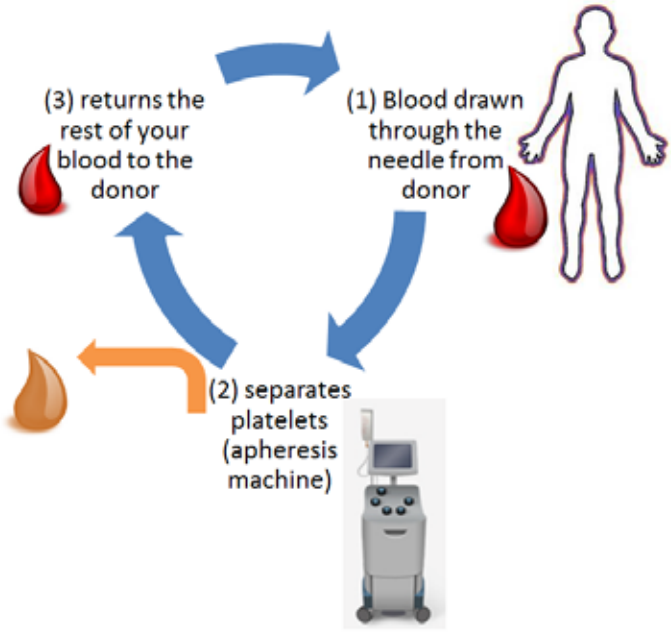


Fig. 2: Process of Single Donor Platelet Formation

two hour pheresis procedure. In the process, platelets and some white cells are removed while the red cells and plasma are returned to the donor. A typical apheresis platelet unit is equal to six of more units of RDPs. (3 to 6 X 10^{11} platelets) (Figure 2).

Here the recipient is exposed only to a single donor. Further the recipient's features such as HLA type matching, CMV status and blood type can be assessed.

The pooled and apheresis platelets contain some amount of WBC, plasma and RBCs. These can give rise to febrile non hemolytic transfusion reactions (FNHTR), alloimmunization, transfusion associated graft-versus host disease (ta-GVHD) & transfusion related acute lung injury (TRALI) in some patients.

Platelet storage and pathogen reduction

Since cooling induces a clustering of VWF receptors on the surface of the platelets leading to morphological changes, platelets are stored at room temperature. The morphologically changed platelets due to the cooling effect are increasingly cleared by hepatic macrophages and result in reduced platelet survival in the recipient.

A disadvantage of room temperature storage is the increased growth of bacteria compared with blood components stored in the refrigerator or freezer. This is reduced by various methods like donor screening for blood borne pathogens, proper skin sterilization, to screen for bacterial contamination etc.

The shelf life of platelets stored at room temperature is 5 days. This is because longer storage increases the risk of bacterial infection.

Indication of platelet transfusion

1. Therapeutic (To treat active bleeding or in preparation for an invasive procedure that would cause bleeding).
2. Prophylactic (To prevent spontaneous bleeding).

Therapeutic indications in an actively bleeding patient:

Platelets should be transfused quickly in patients with thrombocytopenia and active bleeding to keep the platelet count above 50,000/microL in most bleeding situations. It should be kept above 100,000/microL if there is DIC or central nervous system bleeding. Other factors contributing to bleeding like surgical or anatomical defect, fever, infection or inflammation, coagulopathy and acquired platelet function defect should be addressed.

Preparation for an invasive procedure

The typical thresholds for the platelet count for some common procedures are as follows. These are based on retrospective studies of patients who are afebrile and have thrombocytopenia but not coagulopathy.

1. Neuro surgery or ocular surgery – 100,000/microL
2. Most other major surgery – 50,000
3. Endoscopic procedures – 50,000 for therapeutic procedures; 20,000 for low risk diagnostic procedures
4. Central line placement – 20,000
5. Lumbar puncture – 10,000 to 20,000 in patients with hematologic malignancies and greater than 40,000 to 50,000 in patients without hematologic malignancies but lower in patients with ITP
6. Epidural anaesthesia – 80,000
7. Bone marrow aspiration/biopsy – 20,000

Bone marrow studies can be done with lower counts if sufficient pressure (10 – 15 minutes) is applied at the site of the procedure.

Prevention of spontaneous bleeding

Prophylactic transfusion is used to prevent spontaneous bleeding in patients at high risk of bleeding. The threshold for prophylactic transfusion varies depending on the patient and on clinical scenario.

Predictors of spontaneous bleeding

Patients with platelet count more than 50,000 are less likely to bleed but they can bleed sometimes even with platelet counts greater than 50,000.

- The platelet count at which the patient bled previously can be a good predictor for bleeding.
- Mucosal bleeding (wet bleeding) are more predictive than petechial bleeding and ecchymoses.
- Coexisting inflammation, infection and fever increase the risk.
- The underlying condition responsible for the patient's thrombocytopenia may help in estimating the risk of bleeding. Patients with ITP often tolerate very low platelet count without bleeding. Patients

with leukemia and coagulopathy can have bleeding at higher counts (30,000 – 50,000).

- Children are likely to experience bleeding compared with adults with bone marrow suppression.
- Tests for platelet dependent hemostasis like bleeding time, Thromboelastogram (TEG) are not useful in predicting bleeding in thrombocytopenic patients.

Usual practice

Prophylactic platelet transfusion is given to prevent spontaneous bleeding in most afebrile patients with platelet counts less than 10,000 due to bone marrow suppression.

Higher thresholds (30,000) are used in patients who are febrile or septic. For patients with APL (acute promyelocytic leukemia) who have coexisting coagulopathy, the platelet transfusion threshold is 30,000 to 50,000.

For patients with platelet consumption (ITP, DIC) or platelet function disorders, platelets are transfused only for bleeding or in some cases for invasive procedures. For patients with hematological malignancies, HCT (Hemopoietic cell transplantation) and cytotoxic chemotherapy, the threshold is 10,000 to 20,000. For patients with TTP and HIT, platelet transfusion should be given only if they bleed because prophylactic transfusion may cause a slightly increased risk of thrombosis.

Dosing of platelets

A standard dose for prophylactic platelet transfusion is one RDP per 10kg body weight which amounts to 4 – 6 RDP or one SDP. This platelet dosing is expected to increase the platelet count by approximately 30,000/mL within 10 minutes of the infusion. This gradually wanes off after 72 hours. The rate of platelet transfusion (4 – 6 RDP or one SDP) is approximately 20 – 30 minutes.

Complications of platelet transfusion include – infection, TRALI, Transfusion associated circulatory over load (TACO), alloimmunization, allergic and anaphylactic reactions, FNHTR, Ta GVHD and post transfusion purpura.

Platelets express ABO and HLA class 1 antigens. They do not express Rh or HLA class II antigens.

ABO and HLA compatible platelets appear to cause a greater platelet count increment in the recipient and they can be used to improve responses in patients who have become refractory to platelet transfusion due to alloimmunization. Refractoriness to platelet transfusion therapy is said to be present when the desired increment does not occur after one or two transfusions. Platelets can be modified by leukoreduction and irradiation to reduce the complications associated with platelet transfusions.

GRANULOCYTE TRANSFUSION

There is a renewed interest and application of granulocyte transfusion. There were a lot of difficulties in collecting adequate number of viable, functional granulocytes.

Currently granulocytes are harvested from properly selected donors by apheresis after they are stimulated by dexamethasone and G-CSF. Usually it is transfused within a few hours after the collection though it can be stored for 24 hours in room temperature.

The criteria for transfusions are absolute neutrophil count-ANC <500 cells/microL, evidence of bacterial or fungal infections and unresponsiveness to antimicrobial treatment for at least 48 hours. The main indications are neutropenia from chemotherapy or transplantation, aplastic anemia, chronic granulomatous disease and neonatal sepsis. Prophylactic GTX (granulocyte transfusion) is controversial.

Complications are pulmonary adverse reaction, transfusion associated GVHD, alloimmunization and infection.

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