Chapter

83 Blood Component Therapy

JINA BHATTACHARRYA, SUNU LAZAR CYRIAC

Today's transfusion medicine practice aims at providing the specific component of the blood required; this process of transfusing only the portion of the blood needed by the patient is called blood component therapy. This approach allows for optimal use of limited community resource. Transfusion of whole blood has become a rarity now except in certain situations. Blood component therapy has become an integral part of treatment of many diseases in all fields of medicine especially in hematology, hemato-oncology and internal medicine practice. A unit of blood can be separated into different components[1] as shown in Table 1. Red blood cell and platelets are the most frequently used components of blood. Uses of different components are discussed briefly here.

RED BLOOD CELL COMPONENTS

Amongst the red blood cell components (Table 2)[2], red cell concentrates are the most commonly used component. This is the product of choice for correction of an isolated defect in oxygen carrying capacity by raising the hemoglobin concentration in patients with anemia.

There are no reliable parameters to guide need for red cell transfusion. Significant variation exists in the use of red cell transfusions without any correlation with patient characteristics resulting in widespread inappropriate use.

The principles of red cell transfusion should be[3]:

a. Awareness of appropriate indications and about the risks and benefits of transfusion.
b. Establishment of the cause of anemia. Red cell transfusion should not be given when alternative treatment options exist, e.g. iron deficiency anemia, megaloblastic anemia and autoimmune hemolytic anemia etc.
c. Application of clinical judgment which plays a pivotal role as there is no universal trigger.
d. Use of crystalloids and synthetic colloids should be for volume replacement in acute blood, loss except in losses exceeding 40%.

Recommended indications for transfusions based on these principles are:

- **Acute blood loss**: The need for transfusion is based on:
  - — *Estimation of loss of circulating volume*: >40% loss (2000 ml in an adult) requires replacement with colloid-crystalloid and RBC. In case of volume loss lower than this, transfusion requirement would depend upon preexisting anemia, co-morbid conditions or persistent blood loss.
  - — *Concentration of hemoglobin*: Transfusion trigger is <7 g/dl. No need of blood/RBC transfusion with hemoglobin of >10 g/dl; The strategy is not clear for hemoglobin between 7 g/dl and 10 g/dl. For patients above >65 years of age and patients with co-existing cardiovascular disease the trigger is < 8 g/dl.
- **Critical care patients with anemia**: The transfusion trigger is the same.
- **Peri-operative transfusion**: For surgical clearance, earlier threshold of 10g/dl for surgery is discarded and routine transfusion is no longer advised. Peri-operatively, the objective should be to manage the patient without transfusion. Specific measures that should be taken for this are: treatment of anemia before surgery, discontinuation of anti-platelet

Table 1: Components of blood

Component	*Constituent*	*Indication*	*Dose*	*Precautions*
Fresh frozen plasma (FFP)	All coagulation factors 0.7 –1.0 U/ml of factors II, V, VII, VIII, IX, X, XI, XII, XIII and 2.5 mg/ml fibrinogen	Treatment of any coagulation factor deficiency (prolonged PT, APTT),In TTP	15 ml / kg or 1bag per 10 kg as initial treatment (constitute 25-30% replacement therapy for coagulation factors)	Infuse soon after thawing, ABO compatibility needed
Cryoprecipitate	Fibrinogen (150 mg/bag), Factor VIII (80-120 units/ bag), Factor XIII, vWF	Fibrinogen deficiency or consumption; Hemophilia A; vWD; Ftr XIII deficiency	1 bag per 5 kg will raise fibrinogen levels by 70 mg/dl	
Random donor Platelets (RDP)	Platelets, contains at least 5.5 x1010 platelets	Thrombocytopenia	1 unit raise counts by 5-10,000/mm^3 Dose 1unit /10 kg to ↑ count by 30—50,000/mm^3	Infuse rapidly, do NOT refrigerate prior to transfusion
Single donor platelets (SDP)	Platelets, contains at least 3 x 1011 platelets	Thrombocyto-penia	One collection is equivalent to approximately 6 units of random platelets	Precautions as for RDP
Factor VIII concentrates	Factor VIII (Plasma derived products contain vWF also)	Hemophilia, (Plasma derived may be used for vWD)	1 unit / kg raises level by 2%. Half-life is 8 hr	Dose to be given 12 hrly
Factor IX concentrates	Factor IX	Hemophilia B	1 unit / kg raises level by 1%. Half-life is 24 hr	Dose is given once a day
Fresh blood	All components of blood	To replace acute blood loss	As indicated	Not a good source for platelet/ factors

Table 2: Red blood cell components

Component	*Indications*
Whole Blood	Combined red cells and volume deficit, e.g. massive hemorrhage; exchange transfusion
Red blood cells	Red cell deficit
Leukocyte reduced red blood cells	Prevention of febrile reaction/ alloimmunization
Washed red cells	Prevention of allergic reaction
Frozen red cells	Autologous storage for postponed surgery

agents, reversal of anticoagulants, autologous transfusion and use of pharmaceutical agents to reduce bleeding. Trigger for transfusion perioperatively is hemoglobin of 7 g/dl.

- **Thalassemia:** Long-term transfusion strategy is taken for patients with beta thalassemia where the aim is to maintain hemoglobin of 10 g/dl or more.

Response to Red Cell Transfusion

Response to 1 unit of red cell varies from patient to patient. In the absence of hemolysis, one unit of blood is expected to raise the hemoglobin by 1g/dl and hematocrit by 3% and this is measurable 24 hours after transfusion.

Other red cell components are shown in Table 2.

PLATELET TRANSFUSION

Platelet is a very important blood component especially in hemato-oncological practice without which the present day chemotherapy would not be possible. Platelets are available in two form.

1. **Pooled random donor platelet concentrate (RDP)** prepared from whole blood or buffy coat contain 5.5- 7.5 × 10^{10} platelet per unit.
2. **Single donor platelet (SDP)** collected by aphaeresis containing ~ 3x10^{11} platelet or equivalent to 6 RDPs/ bag . The platelet count should be more that 240x10^9.

Both are therapeutically equivalent in terms of post transfusion platelet increments and hemostatic effectiveness[4].

Platelet units are stored at room temperature between 20 and 24°C and kept under gentle horizontal agitation to maintain viability. Recommended storage period is 5 days; beyond this risk of bacterial overgrowth

is very high. In an open system, the shelf-life is reduced to 24 hours; however, the component should be used within 4 hours of opening. Platelet preparations are never to be kept in refrigerator. All the platelet preparations should be gamma irradiated before transfusion with a minimum dose of 25Gy or otherwise bedside platelet filters should be used. Bacterial infection is a serious complication of platelet transfusion which is stored for more than 3 days. Reasons are:

- Bacteria can enter from donor skin at the time of collection.
- Platelet stored in oxygen permeable bags at 22°C helps to preserve platelet function but encourages bacterial overgrowth.

The dose of platelet is one RDP/10 kg of body weight i.e. 4-6 RDP (one SDP) for an adult and 10-15 ml/kg for children. The same should be transfused rapidly over 30 minutes; in pediatric patients the rate should be 20-30 ml/kg/hour.

Indications for Platelet Transfusion

Platelet transfusion is indicated prophylactically for prevention and therapeutically to stop bleeding in patients with thrombocytopenia or platelet function defects. Platelet transfusion is associated with various risk factors, e.g. alloimmunization, transmission of bacterial infection, allergic reaction, transfusion related acute lung injury (TRALI). Hence, the decision to transfuse platelets prophylactically should be based on assessment of risk versus benefit. The guidelines for platelet transfusion thus, are[4,5]:

- To prevent bleeding the trigger for prophylactic platelet transfusion in acute leukemias and stem cell transplantation setting is 10×10^9/l without any additional risk factors like sepsis, coagulopathy, bleeding, use of antibiotics etc. Currently the trigger has been further lowered to 5×10^9/l without any risk factors in centers where platelet is easily available with good monitoring support.
- The trigger for patients with acute promyelocytic leukemia however is 20,000/cumm due to the higher chances of intracerebral bleeds.
- In patients with chronic stable thrombocytopenia, aplastic anemia and myelodysplastic syndromes prophylactic platelet transfusion is discouraged since they remain free of serious hemorrhage even with a platelet count of less than 10,000/cumm of blood.
- The recommended trigger is at least 50,000/cumm of blood for procedures like lumbar puncture, epidural anesthesia, upper gastrointestinal endoscopy, transbronchial biopsy, laparotomy. For surgeries involving the eyes and brain the trigger should be 100,000/cumm. It should be emphasized that the platelet count must be checked just before surgery to ensure that required rise in count has occurred. For procedures like bone marrow aspiration and bone marrow biopsy, no support is needed; adequate local pressure suffices.
- In platelet functional defect platelet transfusion is indicated in case of active bleeding only, after removing the underlying cause of bleeding if any, e.g. withdrawing of antiplatelet agents, correcting anemia etc. Before considering platelet transfusion, measures like DDAVP (Inj. Desmopressin) are to be used to stop the bleeding.
- In ITP platelet transfusion is not indicated except in life-threatening bleeding[4].
- In TTP and heparin induced thrombocytopenia (HIT) platelet transfusion is relatively contraindicated as this may precipitate thrombotic episodes.

Platelet Selection

Preferably ABO compatible and Rh-D compatible blood has to be used because non-identical transfusion is associated with poorer response. Rh-D non-identical transfusion in child bearing age should follow anti-Rh-D immunoglobulin[6].

Monitoring Platelet Response

This is done by the following ways.

- Percent platelet recovery

$$= \frac{\text{Platelet increment } (\times 10^9/\text{L}) \times \text{blood vol} \times 100}{\text{Platelet dose transfused } (\times 10^{11})}$$

- A successful transfusion requires a recovery of 67%. For minimum platelet recovery, a recovery of at least >30% at 1 h; > 20% at 24 h is required.

Practically to monitor the effect of platelet transfusion we see platelet increment by subtracting pre-transfusion platelet count from 1hr post-transfusion count (= 10 min post transfusion count)[7].

Platelet Refractoriness

Platelet Refractoriness is defined when platelet counts do not rise above trigger, despite repeated transfusions and when there is poor increment, even after 2 ABO-compatible transfusions (stored less than 72h). In presence of this prophylactic platelet transfusion is avoided[6].

GRANULOCYTE TRANSFUSION

- Granulocyte transfusion (ABO compatible) has increasingly been used in the treatment of life-threatening bacterial and fungal infections during severe neutropenia. It is collected by leukopheresis using cell separator yielding 80×10^9 neutrophils. The half-life of the neutrophil is approximately 7 hour. It needs to be given daily at the dosage of $40\text{-}60 \times 10^9$ cells/day for at least 4 days.
- Increase in peripheral blood neutrophils of the donor by 2-fold and 7-fold is caused by single dose oral dexamethasone(8 mg) and granulocyte-colony stimulating factor (G-CSF, 450-600 µgms) respectively, 12 hrs before leukopheresis.
- The recommended indications for granulocyte transfusion are[8]:
  - — Resistant severe clinical infection in a neutropenic patients with no response to aggressive antibiotic and no recovery of neutrophil count expected for more than 7 days.
  - — Severe infections, e.g. severe systemic infection or neutropenic enterocolitis which is progressing in spite of aggressive treatment with anti-fungal and broad spectrum antibiotic and no recovery of neutrophil count expected for more than 7 days.
- Adverse effect of granulocyte transfusion are fever, chills, minor oxygen desaturation, pulmonary toxicity in 1-5%, and hypotension due to TRALI; it usually occurs when amphotericin B is given concomitantly. Hence, there should be a gap of 8 hour between the two. Because of risk of TA-GVHD, the pack should always be irradiated.

PLASMA DERIVATIVES

Plasma derivatives are made from pooled plasma derived from thousands of donors. Thousands of plasma units are fractionated into number of purified proteins[9]. ***Fraction I*** contains FVIII and fibrinogen, ***fraction II*** contains immunoglobulins and ***fraction V*** contains albumin. ***Fractions III and IV*** contain a number of other coagulation factors and proteins. Since thousands of donors are involved in these pooled plasma products, transmission of infectious agents is possible even after taking all measures to inactivate the infectious agents. Among these derivatives, commonly used products are albumin, coagulation factor concentrate especially F VIII and F IX and intramuscular as well as intravascular immunoglobulins.

Frozen Plasma

Different types of frozen plasmas are available:

1. **Fresh frozen plasma** (FFP): Plasma frozen at -18°C or colder within 6 hours of donation.
2. **F24 plasma**: Plasma frozen at -18°C or colder within 24 hours
3. **Cryosupernatant or cryo-reduced plasma** (CRP): derived when FFP thawed at 4°C; once collected it is refrozen at **-**18^0C or colder
4. **Solvent-detergent treated plasma**
5. **Liquid plasma**: Plasma not immediately frozen as FFP or F24 and stored at 1-6°C. Used for preparation of plasma derivatives like albumin, factor concentrate and immunoglobulins.

Thawed FFP can be stored at 4°C and can be used safely within 24 hours; however when kept at room temperature, must be used within 4 hours.

Indication for Use of Frozen Plasma

Most importantly FFP should never be used as a volume expander or source of nutrients. For single factor deficiency it should only be used when no virus safe factor concentrate is available, e.g. factor V deficiency. Common indications are[10]:

1. Liver disease is the most common indication for FFP transfusion when there is bleeding (which is mostly from an anatomical lesion) in presence of prolonged PT and APTT.
2. Patients receiving large quantities of packed red blood cell transfusion (PRBC), e.g. more than 1 blood volume in 24 hours need FFP because of dilutional coagulopathies. One unit of FFP for every 5 units of PRBC is recommended.
3. Patients with disseminated intravascular coagulation with active bleeding.
4. Rapid reversal of warfarin effect: FFP is not recommended as a routine as functional deficiency of vitamin K-dependent factors get corrected within 48 hours after warfarin is withdrawn. Addition of vitamin K corrects it by 12-18 hours. However in patients with active bleed who require emergency surgery may be given FFP.
5. In thrombotic thrombocytopenic purpura patients simple transfusion or in plasma exchange is the treatment of choice because plasma contain the needed VWF cleavage protease.

Dosage

One unit of FFP derived from a unit of whole blood contain 200-280 ml; apheresis plasma may be as large as 800 ml. On average there is about 0.7-1 unit/ml of coagulation factor activity per ml of FFP and 1-2 mg/ml of fibrinogen. The usual dose is 8-10 ml/kg; frequency depends upon clinical response. FFP should always be ABO compatible.

CRYOPRECIPITATE

Cryoprecipitate is prepared from one unit of FFP thawed at 4°C and the precipitate is then refrozen in 10-15 ml of plasma and stored at -18°C or colder. It contains 80-100 units of F VIII, 100-250 mg of fibrinogen, 50-60 mg of fibronectin and 40-70% of vWF and also F XIII. It is predominantly used to treat F XIII deficiency and fibrinogen deficiency. However, in India due to non-availability and high cost of factor VIII concentrate it has been used for factor substitute in hemophilia and von Willebrand's disease.

COAGULATION FACTOR CONCENTRATE

These are intermediate and high purity plasma derived concentrates and prepared from cryoprecipitate and fresh frozen plasma. Factor VIII and Factor IX concentrates are the commonly used factor concentrates for hemophilia and are used mostly as replacement therapy. The objective of this is to obtain a concentration of the required factor at the bleeding site; this hemostatic level is defined as the lowest plasma concentration of a given coagulation factor required for a normal hemostasis. Hemostatic level of Factor VIII is 25-30 U/dL and factor IX is 15-30 IU /dL. For factor XIII levels as low as 2-8 U/dL is adequate. The dose and duration of treatment depend on site, severity, nature of prophylaxis and half- life of the deficient factor (Tables 3 and 4). One unit of factor VIII concentrate /kg raises the factor level by 2% and for factor IX it is 1%.

Table 3: Half-life and dosage of important factor concentrates

Factor	*Plasma half life*	*Frequency of doses*
VII	5-6 hr	BD or TID
VIII	8-12 hr	BD
IX	18-24 hr	OD
II (Prothrombin)	65 hr	OD or less frequent
I (Fibrinogen)	90 hr	OD or less frequent
V	12-15 hr	OD
X, XI, XII, XIII	36 hr	OD

FIBRIN GLUE AND SEALANTS

This results from a mixture of fibrinogen source (FFP, PRP, heterologous or autologous cryoprecipitate) with bovine thrombin. The hemostasis is achieved with action of thrombin on fibrinogen. This is widely used during surgery to stop bleeding immediately[9].

ALBUMIN

Albumin is available in three forms: 5%, 25% and purified protein fraction. It is heat treated and therefore unable to transmit viruses. It is an excellent growth medium for bacteria, bacterial contamination can lead to febrile and more serious reactions[9].

Intravenous Immunoglobulins

Intravenous immunoglobulins are prepared by fractionation of large pools of human plasma. Its most common clinical use is in acute immune thrombocytopenia with a very low platelet count and active bleeding. Infusion should be started slowly and monitored closely; initially 0.5 ml/kg/hour and then increased gradually

Table 4: Guideline for factor replacement in hemophilia

Site	*Factor level*	*Dose hemophilia A*	*Dose hemophilia B*	*Duration*
Joint	30-70%.	15-35 μ/kg	30-70 μ/kg	1-3 days
Life threatening	80-100%	40-50 μ/kg.	80-100 μ/kg	10-14 days
Surgery	80-100%	40-50 μ/kg	80-100 μ/kg	10-14 days
Oral	20-50%	10-25 μ/kg	25-50 μ/kg	1-2
Gastrointestinal	30-100%	1-50 μ/kg	30-100 μ/kg	2-3
Genitourinary	30-50%	15-25 μ/kg	25-50 μ/kg	1-2
Prophylaxis	50%	25 μ/kg	50 μ/kg	qod or 3 x/wk
Soft tissue	30-50%	15-25 μ/kg	30-50 μ/kg	2-5 days

upto 8-fold. Other uses are Guillain-Barre syndrome, autoimmune hemolytic anemia etc[9].

Hyperimmune Serum

Hyperimmune serum is prepared from large pools of plasma known to contain elevated antibody titers against specific infectious agents. Different types of hyperimmune serum are (i) Anti-thymocyte globulin (ii) Cytomegalovirus immunoglobulin, (iii) Hepatitis B immunoglobulin and (iv) Rh-D immunoglobulins. Indications for use of Rh D Ig are RhD alloimmunized mother, prevent immunization in Rh(D) negative individuals who are given Rh(D) positive component (like platelet) and in immune thrombocytopenia. ATG is indicated in aplastic anemia, renal transplant patients, graft rejection and as a preparative regimen for stem cell transplant.

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