Review Article

Blood component therapy in anaesthetic practice

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In Canada, over one million units of whole blood are collected annually by the Canadian Red Cross Blood Transfusion Service from volunteer donors. Most of these units are separated into components. In addition, large quantities of plasma, white cell concentrates and platelet concentrates are collected by apheresis procedures. With the advent of blood component therapy, each unit of whole blood collected serves the specific needs of several, rather than a single patient. One unit of whole blood can thus be separated into: a red blood cell preparation containing all the red blood cells of a unit of whole blood; a platelet concentrate having approximately 70 per cent of the platelets; and a unit of cryoprecipitate containing approximately 50 per cent of the Factor VIII. The residual plasma is fractionated into various products including albumin, immunoglobulin and preparations of the various clotting factors. This gradual change in blood transfusion practice to the use of specific components has been called the quiet revolution in blood transfusion therapy.¹ Blood component therapy, which plays a very important role in anaesthetic practice, has as its goal the provision of specific blood components to patients, rather than whole blood.

Approximately twenty different blood products are currently available to fulfill patients' specific needs.² Their judicious use will provide for optimal clinical benefit to patients and optimal utilization of the available resources of donor blood. An anaesthetist, in making a decision to use a particular blood product, should be thoroughly aware of the indications, contraindications, and the potential undesirable side effects of the blood product to be used. A prerequisite, therefore, of component therapy is the correct identification of a particular patient's clinical need. It is paradoxical that anaesthetists, who are meticulous in their approach to

fluid and electrolyte balance and in the use of various anaesthetic agents and other drugs, are less discerning in their choice of blood products.

The anaesthetist generally requires blood products to meet three sets of clinical needs: (a) to increase oxygen transport; (b) to expand blood volume; and (c) to control bleeding.

This article is intended to provide guidelines for the use of blood and blood components in these three clinical situations. No attempt will be made to anticipate the blood product needs in every conceivable situation that might be encountered.

Products to increase oxygen transport

The main function of the red blood cells in the circulation is to provide for oxygen transport to tissues. The primary indication, therefore, for the transfusion of blood products containing red blood cells is to improve the capacity for oxygen transport where deficient. As shown in Table I, a number of products, both synthetic and natural, are available which can aid in improving oxygen transport to tissues. These include the various red blood cell suspensions, synthetic oxygen carrying materials (e.g., perfluorochemicals) and chemically modified haemoglobin solutions.³

Red blood cell preparations for transfusion are available in several different formats. These include whole blood, red cell concentrates, frozen-thawed red cells and leukocyte-depleted red cells. The preparation chosen should be appropriate to the specific clinical situation and must take into account product availability, time required for preparation and storage limitations. A comprehensive blood transfusion service will usually have full-scale blood component and plasma fractionation programmes, resulting in only a small proportion of red blood cell preparations remaining as whole blood. Concentrated red cells will therefore be the product most readily available.

Red blood cells are probably transfused more often than they are really indicated. Red blood cell preparations are frequently inappropriately used for blood volume expansion when plasma expanders could have been used. Furthermore, misconceptions about the general therapeutic benefit of blood, particularly whole blood, also leads to misuse. The belief, for example, that wound healing is impaired in anaemic patients and that the use of whole blood is required to promote wound healing, is a gross

TABLE I Products to increase oxygen transport

Red blood cell suspensions
Whole blood
Red cell concentrates
Frozen-thawed red cells
Leukocyte-depleted red cells
Synthetic oxygen carriers
Perfluorochemicals
Chemically modified haemoglobin solutions

example of misuse. Clinical experience, with military casualties, has shown that a patient can lose up to 30–40 per cent of his blood volume without requiring red blood cell replacement, providing that the blood volume is replaced by other means, such as plasma substitutes or electrolytes.⁴ Despite much experience, however, it is difficult to delineate absolute indications for red cell transfusion. Nonetheless, in assessing the need for the replacement of red blood cells in a particular clinical situation, a number of factors should be considered. These include the assessment of the rate and magnitude of blood loss, the state of tissue perfusion, and whether the desired result can be achieved without the transfusion of blood products, particularly red blood cells. In addition, the potential complications of the intended blood transfusion must be balanced against the expected gain. The following criteria (modified from Mitchell⁵) are suggested for the appropriate use of red blood cells for transfusion:

1. Massive blood loss requires the rapid replacement of both red blood cells and colloid (plasma).
2. Acute limited blood loss, where significant anaemia is not a likely result, can usually be treated by volume replacement with colloid and/or electrolytes.
3. Preoperative blood transfusion to elevate an intermediate haemoglobin level or to improve the patient's general condition is rarely indicated. It should be performed only if the surgery is urgent, and the patient's clinical state would otherwise preclude surgical intervention.
4. The transfusion of red blood cells postoperatively should be primarily for the purpose of providing improved oxygen transport to tissues, not to improve an arbitrary haemoglobin level.

(a) *Whole blood*

A standard unit of *whole blood* consists of approxi-

mately 450 ml of blood taken in 63 ml of anticoagulant consisting of citrate, phosphate, dextrose and adenine (CPDA-1). Red blood cells in CPDA-1 may be stored (either as whole blood or as red cell concentrates) at 4° C for up to 35 days. During the storage period, there are changes in red cell function and viability which are not significant in most clinical situations. Even at the end of a 35-day storage period, at least 70 per cent of the red blood cells present in a particular unit of blood are recoverable in the circulation and survive normally. During storage there is a progressive loss of labile components (certain coagulation factors, platelets and white cells). Concomitantly there is an accumulation of hydrogen and potassium ions in the plasma. The clinical situation requiring an improvement both in oxygen carrying capacity and volume simultaneously may be treated with *whole blood*, and in some situations may be the treatment of choice; however, the combination of concentrated red cells and colloid or electrolyte solutions can be equally effective. In many situations, the use of *red cell concentrates* in combination with other components may be preferable, as this approach would provide some of the labile substances which may not be present in stored whole blood.

Occasionally a clinician requests *fresh whole blood*. Fresh whole blood is not a transfusion product that can be safely and readily provided, nor is it ever really indicated. Most clinical situations with a need for fresh whole blood can be met equally well with the informed use of blood components.

(b) *Red cell concentrates*

Red cell concentrates are suspensions of red cells prepared by removing approximately 200 ml of plasma from whole blood. Table II compares the properties of *red cell concentrates* with that of whole blood. A full-scale blood component and plasma fractionation programme necessarily results in the production of a high proportion of red cell concentrates. Red cell concentrates are an effective means of correcting anaemia. Using red cell concentrates, more red blood cells can be infused to a recipient for each unit volume transfused than whole blood; thus the risk of hypervolemia is reduced, a particular concern in the anaemic elderly patient. For all of these reasons, red cell concen-

TABLE II Comparison between a red cell concentrate (RCC) and a unit of whole blood (approximate mean values)

	RCC	Whole blood
Total volume (ml)	300	500
Red cell volume (ml)	200	200
Plasma volume (ml)	100	300
Haematocrit (%)	70	40
Albumin content (g)	4	12

trates should be viewed as the standard format of issue of red blood cells for transfusion.

The main differences between a unit of *whole blood* and a *red cell concentrate* unit is the volume of plasma in which the red blood cells are suspended (Table II). Whole blood has a haematocrit of approximately 40 per cent, whereas red cell concentrates have a haematocrit of approximately 70 per cent. The higher haematocrit of red cell concentrates may result in a slow flow rate due to increased viscosity. If there is a need to increase the rate of flow of a red cell concentrate to a patient, the haematocrit may be reduced by the addition of isotonic saline to the red cell concentrates. The use of a Y-shaped blood administration set will facilitate the addition of saline to the red cell concentrate. Saline should be added, at the bedside, just prior to administration of the red cell concentrate to the patient. The addition of saline in the blood bank is contraindicated as opening the unit may result in the introduction of bacteria to that unit of red blood cells, and any delay in initiating the transfusion will enhance the opportunity for bacterial multiplication.

(c) *Frozen-thawed red cells*

Red blood cells can be frozen with the use of special cryopreservation techniques.⁶ Such techniques permit the storage of red blood cells for up to ten years. The facilities for the preservation of red blood cells in the frozen state are available in many blood transfusion centres. The freezing, storing and reconstitution of frozen red blood cells is, however, expensive and *frozen-thawed red cells* are recommended only in special circumstances. These include: (a) the provision of red blood cells to individuals with rare blood types; (b) autotransfusion to individuals with red blood cell alloantibodies which make the provision of compatible

donor blood difficult; and (c) clinical situations with the need to minimize alloimmunization in individuals undergoing chronic transfusion therapy. Reconstituted frozen-thawed red cells should not be stored for periods longer than 24 hours as the processing (freezing and thawing) requires the unit to be entered and thus potentially to be contaminated.

(d) *Leukocyte-depleted red cells*

Standard units of *whole blood* or *red cell concentrates* contain most of the leukocytes present in the original blood donation. These white cells are viable for only a short period and may be present either intact or fragmented, depending on the age of the unit of blood. In most transfusion situations, the presence of white cells is of no consequence. Occasionally, however, it may be desirable to transfuse a patient with a red cell preparation from which the white cells have been removed.

Leukocyte-depleted red cells may be indicated in individuals with a history of severe febrile non-haemolytic transfusion reactions during or following transfusion. A number of different techniques exist for the removal of leukocytes from red cell preparations.⁷⁻⁹ The use of costly wash techniques or special filters is not indicated for the majority of transfusions.^{10,11}

Recently, microaggregate filters have been recommended for the removal of leukocytes and the microaggregates present in stored blood. During storage, the number of microaggregates present in blood increases progressively; these consist of aggregates of platelets, white cells and fibrin strands. Experimental work in dogs indicates that massive blood transfusion can result in pulmonary insufficiency due to microembolization in the pulmonary circulation. Standard blood filters remove particles greater than 170 μ and several effective types of microaggregate filters are available to remove aggregates greater than 40 μ ; however, they are expensive compared to standard 170 μ filters. No clear-cut clinical evidence exists in humans that microfiltration is necessary even in patients receiving massive blood transfusion. Several recent studies have demonstrated no benefit of microfiltration in man.¹²

(e) *Synthetic oxygen carriers*

Significant progress has been made in the develop-

ment of synthetic oxygen-carrying agents which can be used for short periods in place of, or in conjunction with, red blood cells. Two classes of oxygen-carrying substances exist; one synthetic, the perfluorochemicals; and the other derived from haemoglobin.^{3,13} The perfluorochemicals are fluorinated hydrocarbons which are byproducts of the petroleum industry. The perfluorochemicals dissolve oxygen very readily; however, they are poorly soluble in plasma and thus require emulsification for use. Emulsification results in the formation of 0.2 μ micelles and, to maintain osmolarity, other agents are added. Perfluorochemicals must be stored in the frozen state as they are unstable in the unfrozen state. Fluosol-DA, the most recent formulation of perfluorochemical, has been extensively studied in animals and is presently undergoing clinical trial in man. Fluosol-DA is not yet licensed for human use in North America and is only available to designated investigators for use in special clinical situations. Preliminary human and animal studies show that perfluorochemicals remain in the intravascular space for only short periods of time (less than 24 hours) and their long-term effects have not been fully evaluated. Occasional side effects have been reported with human use.³ Of great promise is the potential use of perfluorochemicals as oxygen carrying agents in the treatment of ischaemia resulting from vascular disease. In experimental animals, perfluorochemicals have been shown to reduce the size of experimentally-induced myocardial and cerebral infarction.^{14,15}

(f) *Chemically modified haemoglobin solutions*

Chemically modified haemoglobin solutions represent another class of substances which potentially can be used to improve oxygen transport in place of intact viable red blood cells.³ Unmodified haemoglobin solutions have a very short half life when free in the circulation and are nephrotoxic. In order to use free haemoglobin effectively as an oxygen carrier, it must be modified. The cross-linking of haemoglobin molecules results in a molecule which has a longer intravascular survival.³ By adding pyridoxal phosphate and glutaraldehyde to haemoglobin, a polymerized haemoglobin molecule is produced which can carry oxygen and remain in the circulation for approximately 24 hours. Such haemoglobin solutions have proven of value for

TABLE III Products available for volume expansion

Albumin
5% solution
25% solution
Plasma
Stored plasma
Frozen plasma
Fresh frozen plasma
Plasma protein fraction
Synthetic colloids
Electrolyte solutions
Red cell suspensions

oxygen delivery in animal studies but have not yet been used in humans.

Products available for volume replacement

When oxygen-carrying capacity is adequate but circulating volume is reduced, the blood volume can be expanded using a variety of agents available. These are outlined in Table III. The available products include plasma, albumin, and electrolyte solutions. In addition, as indicated earlier, red cell products may be used for volume expansion. Red cell suspensions should, however, be used only when increased oxygen transport is also required. The use of whole blood or other red blood cell suspensions may be indicated for both volume replacement and oxygen-carrying replacement in clinical situations where there is a large volume acute blood loss.

Several forms of plasma differing mainly in their content of labile clotting factors are currently available. These include *stored plasma*, *frozen plasma*, and *fresh frozen plasma*. Plasma does not require cross-matching prior to use but should be ABO compatible with the recipient's ABO group. If the plasma product is stored in the frozen state, a thawing period of approximately 30 minutes is required. The careful consideration of therapeutic goals and the content of the plasma preparations will ensure that effective treatment will be given and valuable Factor VIII containing plasma conserved.

(a) *Stored plasma*

Stored plasma is obtained from whole blood during the first 72 hours of storage at 4° C or derived from supernatant plasma after cryoprecipitate produc-

tion. *Stored plasma* contains reduced levels of the labile coagulation factors, Factors V and VIII. *Stored plasma* may be stored in the liquid state at 4° C for 35 days or in the frozen state at -30° C for 12 months. When stored unfrozen, it is available for immediate use. *Stored plasma* is indicated for patients requiring volume or protein replacement and in situations requiring the replacement of non-labile clotting factors. It is also recommended for extra-corporeal pump priming, plasma exchange, hypovolemic shock, and burns.

(b) *Frozen plasma*

Frozen plasma is separated from whole blood between 12 and 24 hours after collection of whole blood and contains approximately 50 per cent of the original Factor VIII (and Factor V) contained in fresh blood. *Frozen plasma* may be stored in the frozen state at -30° C for 12 months and is an adequate source of all the coagulation factors for the treatment of mild and moderate coagulation factor deficiencies. Donor blood collection patterns make available large quantities of plasma, fulfilling the specifications of frozen plasma. Appropriate clinical use of frozen plasma conserves fresh frozen plasma for fractionation and for other specific clinical use. *Frozen plasma*, rather than *fresh frozen plasma*, is indicated as replacement for most patients undergoing intensive plasma exchange.

(c) *Fresh frozen plasma*

Fresh frozen plasma (FFP) is prepared from fresh whole blood within 12 hours of collection from the blood donor. Prompt, rapid freezing of the plasma preserves the labile coagulation factors at maximum levels. *Fresh frozen plasma* also represents the starting material for the production of specific clotting factor concentrates and other plasma derivatives. It is not required in most clinical situations, particularly those requiring only volume replacement. *Fresh frozen plasma* contains adequate Factors VIII and V levels for the treatment of mild and moderate clotting factor deficiencies of either inherited, acquired or dilutional types.

(d) *Albumin*

Albumin is one of the most important and abundant plasma components. Albumin, which has a molecular weight of approximately 65,000 daltons, serves primarily to maintain the capillary osmotic pressure

and to act as a carrier protein for various drugs, hormones, enzymes, and metabolites. The concentration of albumin in the circulating plasma is determined by the relative rates of synthesis and catabolism. Normally, approximately 50 grams of albumin is synthesized and metabolized daily. Hypoalbuminaemia may thus be the result of pathophysiological processes affecting either.

Albumin, for transfusion, is generally prepared by cold ethanol fractionation of pooled normal plasma. It is available in concentrations of either 50 or 250 g/litre, in several volume presentations. Both concentrations have a physiological pH and a sodium content of approximately 145 mEq/litre. Thus, the more concentrated albumin preparations contain less sodium relative to albumin. There is no risk of hepatitis with albumin use as it is heated to 60° C for ten hours during manufacture, a temperature which destroys the agents which cause viral hepatitis. Albumin preparations contain neither coagulation factors nor blood group antibodies.

(e) *Plasma protein fraction*

An albumin preparation called *plasma protein fraction* (PPF) is available in some countries which contains approximately 85 per cent albumin and 15 per cent other plasma proteins, primarily alpha and beta globulins. PPF thus contains primarily albumin and has the same therapeutic indications as albumin. There is no advantage to the use of PPF over albumin. PPF is not produced or distributed by the Canadian Red Cross Blood Transfusion Service.

(f) *Synthetic colloid solutions*

There are a number of colloid solutions of non-human origin that can serve as blood volume expanders. None, however, has as sustained an oncotic effect as albumin nor combines transport function with oncotic effect. Numerous undesirable effects have been reported with their use. The various synthetic colloids available are listed in Table IV along with their potential side effects.

Blood products available to correct haemostatic defects

Bleeding during surgery may result from qualitative or quantitative defects in one or more of the three mechanisms which contribute to normal haemostasis (platelets, coagulation factors or the vessel wall). An attempt should be made to identify which

TABLE IV Synthetic colloids available for blood volume expansion and their potential side effects

<i>Synthetic Colloid</i>	<i>Potential side effects</i>
Dextran	Erythrocyte rouleaux. Haemostatic abnormalities.
Gelatin	Erythrocyte rouleaux.
Hydroxyethyl starch	Erythrocyte rouleaux. Haemostatic disorders. Prolonged retention. Hyperamylasaemia.
Polyvinylpyrrolidone	Erythrocyte rouleaux. Prolonged retention in the reticuloendothelial system.
Stroma-free haemoglobin	Renal damage. Hypercoagulability from residual membrane lipids.

component or components are deficient or defective. A variety of products are available to control bleeding due to the deficiency of these haemostatic elements (see Table V). Platelets and some of the coagulation factors are extremely labile during storage and are not present in clinically useful quantities in stored whole blood or red cell concentrates. Fresh whole blood contains all the necessary factors required for normal haemostasis but cannot provide adequate quantities of the desired coagulation factors or platelets without risking circulatory overload. Logistics of supply further complicate the situation. The precise nature of each bleeding disorder should be determined and, wherever possible, specific component therapy instituted. The use of whole blood or *fresh frozen plasma* in the treatment of a specific deficiency is wasteful and generally less effective than precise replacement (see Table VI). In the anaesthetic situation, the most

TABLE V Blood products available to correct haemostatic defects

Platelet concentrates
Plasma
Frozen plasma
Fresh frozen plasma
Stored plasma
Cryoprecipitate
Coagulation factor concentrates
Factor VIII
Factor IX

TABLE VI Blood products for use in the treatment of specific coagulation factor deficiencies

Fibrinogen deficiency	Cryoprecipitate Stored plasma
Factor V deficiency	Fresh frozen plasma
Factor VII deficiency	Factor IX complex (II, VII, IX, X) Stored plasma
Factor VIII deficiency	Factor VIII concentrate (AHF) Cryoprecipitate Fresh frozen plasma
von Willebrand's disease	Cryoprecipitate Fresh frozen plasma
Factor IX deficiency	Factor IX complex (II, VII, IX, X) Stored plasma
Factor XIII deficiency	Stored plasma

common haemostatic defect is that due to the surgical trauma (inadequate surgical haemostasis), not due to a deficiency of the clotting factors or platelets. If a haemostatic deficiency exists, the most common is due to dilution of circulating coagulation factors by the massive transfusion of stored blood. In this situation, *frozen plasma* can supply adequate levels of all the necessary coagulation factors except platelets. In addition to the various types of plasma, the following blood components and fractions are also readily available.

(a) Platelet concentrates

Platelets may be provided to individuals who are deficient in this component by the use of *platelet concentrates*.¹⁶ Each platelet concentrate unit derived from a unit of fresh whole blood is usually prepared in a volume of approximately 50 ml of plasma. When collected in the recently developed packs, platelet concentrates may be stored in this volume for up to five days. Platelet concentrates are stored at 22° C with continuous agitation. Each unit of a platelet concentrate contains an average 6×10^{10} viable platelets.

From clinical experience, it is known that few patients with platelet counts greater than $40 \times 10^9/L$ bleed spontaneously unless they have a concomitant defect in platelet function. Not infrequently during surgery the platelet counts will drop due to increased utilization for haemostatic plug formation or due to dilution by the infusion of blood products. Most patients have adequate marrow reserve to enable a prompt physiological replacement of mild

to moderate platelet reduction without platelet transfusion. Platelet transfusions may be indicated in patients who continue to bleed during surgery despite adequate surgical haemostasis where either a qualitative or quantitative platelet defect is present. The appropriate number of units of platelet concentrate required are pooled prior to administration through a standard filter. As a general rule, one unit of a platelet concentrate will raise the platelet count in an adult by $5 \times 10^9/L$. A variety of factors may influence the *in vivo* recovery of platelets following infusion including infection, platelet alloantibodies, splenomegaly and fever.

(b) Cryoprecipitate

Cryoprecipitate is a plasma concentrate consisting primarily of Factor VIII and fibrinogen in approximately 10 ml of plasma. Other plasma proteins are present in the concentration usually found in normal plasma. A single unit of *cryoprecipitate* contains approximately 100 clotting units of Factor VIII and 250 mg of fibrinogen. A clotting unit of Factor VIII is the amount of Factor VIII in 1 ml of fresh normal plasma. *Cryoprecipitate* is stored frozen and can be prepared for infusion relatively easily with complete thawing achieved within ten minutes at 37° C. Temperatures in excess of 37° C cause a loss of Factor VIII activity.

Cryoprecipitate is generally recommended in those clinical circumstances in which either Factor VIII or fibrinogen is clinically indicated. An average treatment dose in adult patients requiring either Factor VIII or fibrinogen is eight or ten units of *cryoprecipitate*. The average adult responds with an increase in two per cent of the Factor VIII level for each unit of *cryoprecipitate* infused. The most satisfactory way to judge the amount required, however, is to measure the patient's circulating Factor VIII level before subsequent treatment.

Fibronectin is also concentrated in *cryoprecipitate*.¹⁷ Fibronectin has been recommended to improve the immune status of certain patients postoperatively. To date, no clinical studies have proven that fibronectin is of clinical benefit in this situation and the use of *cryoprecipitate* as a source of fibronectin is unjustified at this time.¹⁸

(c) Coagulation factor concentrates

Coagulation factor preparations in concentrated lyophilized form are indicated primarily for use in

patients who are congenitally deficient in the various individual coagulation factors. Use of these concentrates for mild acquired deficiencies is contraindicated because of the high risk of hepatitis associated with the use of these preparations. Mild coagulation factor deficiencies should be treated with frozen or fresh frozen plasma. The levels of the individual factors needed for effective haemostasis is different for each coagulation factor. Table VI lists the products that are available for use in the treatment of specific congenital bleeding disorders.

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