Review Article

Perioperative haemotherapy: I. Indications for blood component transfusion

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The practice of transfusion medicine has undergone substantial change over the last decade. Much of the impetus for the change has come from the isolation of human immunodeficiency virus (HIV) and the linkage of HIV transmission to blood transfusion. The purpose of this paper is to collate and review the literature relating to the indications for blood transfusion and provide recommendations for the appropriate utilization of blood products. Peer-reviewed and published studies and reviews relating to aspects of clinical blood transfusion were identified through computer searches and searching of the bibliographies of identified articles. Emphasis was placed on the literature published within the last decade and particularly in the years 1985–91. Material was chosen which was of proved clinical importance and in which findings were consistent among different investigators or different centres. Less emphasis was placed on material reporting new findings of uncertain clinical relevance or findings that were not consistent with majority reports. It is concluded that the only indication for red cell transfusion is to increase the oxygen carrying capacity of the blood and that an adjustment downwards in the haemoglobin concentration at which blood is transfused (transfusion trigger) from the traditional level of 100 $g \cdot L^{-1}$ is supported by the physiological and clinical data. Perioperative haemoglobin concentrations of 80 $g \cdot L^{-1}$ are acceptable in otherwise healthy young patients. The transfusion trigger should be adjusted upwards from this in medically compromised patients and in the elderly (> 60 yr). Fresh frozen plasma (FFP) is only indicated when there are documented deficiencies of coagulation factors. Platelet concentrates (PC) are indicated for the treatment of clinical coagulopathy resulting from thrombocytopaenia or platelet dysfunction. Routine or prophylactic administration of either FFP or PC after cardiopulmonary bypass or during resuscitation from haemorrhage is not indicated.

Les indications de transfusion sanguine ont été considérablement modifiées au cours de la dernière décennie. La découverte du virus de l'immunodéficience humaine (HIV) et la possibilité de transmission de ce virus par la transfusion ont largement contribué à cette modification. Le but de ce travail est de réviser la littérature concernant les indications de transfusion sanguine et de faire une synthèse qui permet d'établir des recommandations appropriées à l'utilisation des différents produits sanguins. La révision du sujet est faite à partir d'articles retrouvés par recherche sur ordinateur et à partir d'articles cités dans la bibliographie de différents travaux. Les articles publiés durant la dernière décennie, particulièrement entre 1985 et 1991, forment la principale source de références de ce travail. L'emphase est surtout mise sur l'information clinique prouvée, faisant l'unanimité parmi les chercheurs. Les études cliniques aux résultats douteux ou non reproductibles d'une étude à l'autre reçoivent peu d'attention. Il est conclu que la seule indication de transfusion de globules rouges est le besoin d'augmenter la capacité de transport en oxygène, et que la concentration d'hémoglobine limite indiquant la nécessité de transfusion est inférieure à 100 $g \cdot L^{-1}$. Cette conclusion est soutenue par plusieurs concepts physiologiques et plusieurs rapports cliniques. Une concentration d'hémoglobine de 80 $g \cdot L^{-1}$ durant la période périopératoire est acceptable pour les jeunes patients en santé. Cette concentration limite acceptable doit être augmentée pour les patients âgés de plus de 60 ans et pour ceux dans un état précaire. L'utilisation du plasma frais congelé est indiquée seulement en présence d'un déficit documenté en facteurs de coagulation. Les concentrés de plaquettes sont indiqués seulement pour le traitement des congulopathies secondaires à une thrombocytopénie ou à une dysfonction plaquettaire. L'administration automatique ou prophylactique de plaquettes et de plasma frais congelé après une chirurgie cardiaque ou durant le traitement d'une hémorragie est.

Key words
BLOOD: anaemia, haemodilution, loss, replacement;
TRANSFUSION: stored blood.

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It was, until recently, accepted that no patient should be subjected to elective surgery unless the preoperative haemoglobin concentration was 100 g · L^{-1} and transfusion practice was administered accordingly.[1] The risks, real and perceived, of transfusion-associated infectious disease have forced a reassessment of transfusion practice and this has resulted in increased efforts to limit the use of homologous blood transfusions.[2] The simplest method of reducing the incidence of homologous blood transfusion is to withhold transfusion until more severe levels of anaemia are reached. However, the optimum threshold for the initiation of transfusion therapy has not been defined and clearly, the haemoglobin concentration cannot be permitted to decrease to levels such that tissue oxygen delivery (DO_2) or consumption (VO_2) are compromised. The purpose of the following discussion is to review the physiological data that determine safe levels of anaemia in both healthy and compromised patient populations and outline appropriate perioperative blood component utilization. The perioperative use of packed red cells, platelet concentrates and fresh frozen plasma will be reviewed. Although it is recognized that autologous blood predonation programmes and techniques and drugs that allow for reduced operative blood losses or increased autologous blood salvage are important in reducing homologous blood requirements, these will not be discussed.

Blood rheology and oxygen delivery

Tissue oxygen delivery (DO_2) is the product of blood flow and arterial oxygen content and at the whole body level are represented by the product of cardiac output and the arterial oxygen content. Blood flow is determined by the resistance to flow in the vascular bed and the perfusion pressure driving flow through the bed. Resistance to flow is related linearly to the length of the vessels and inversely to the fourth power of the radii of the vessels. Finally, the fluid medium itself may contribute to resistance to flow. A Newtonian fluid is one for which the flow increases in direct proportion to the force exerted upon it such that there is a linear relationship between perfusion pressure and flow. Blood is a non-Newtonian fluid and is most

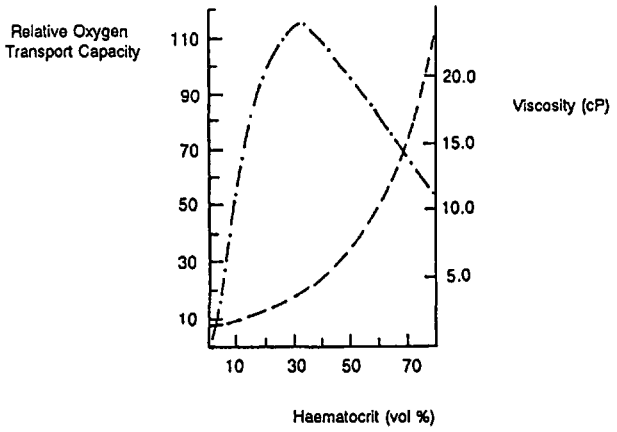

FIGURE The influence of the haematocrit on both viscosity (dashed line) and relative oxygen transport capacity (dashed-dotted line) as a percentage is displayed. Peak oxygen transport capacity occurs at a haematocrit of 30. Below this haematocrit, oxygen transport capacity declines as a result of decreased blood carriage of oxygen. Above this haematocrit, capacity declines as a result of the altered rheological characteristics of the blood and the resultant decreased flows in the microcirculation.

resistant to flow (highest viscosity) at lower flow rates, thus requiring more pressure (defined as shear force) to maintain flow. As the flow rate (defined as shear rate) increases, the shearing force required to maintain flow decreases. Thus, blood has its highest viscosity in venules and its lowest viscosity in the aorta.

The higher viscosity at low shear rates is partly due to red cell aggregation in slowly flowing blood. Viscosity, independent of shear rate, is primarily a function of red cell concentration (Figure). Reduction in haematocrit decreases blood viscosity, reduces the impedance to flow and also the shearing force required to maintain flow at any given shear rate. At lower shear rates, such as those found in the postcapillary venules, a reduction in haematocrit from 40% to 20% results in a reduction in viscosity that is eight times greater than the viscosity reduction measured in the aorta with a similar haematocrit change.[3] Decreasing the haematocrit will have a more profound effect on lowering the viscosity in low flow situations such as the venous system.

The increased tissue blood flow resulting from the lower viscosity must be sufficient to balance the lower oxygen carrying capacity for a net gain in tissue oxygen delivery (DO_2). The optimal haematocrit would be the level which would allow for the greatest DO_2 at the lowest energy cost to the organism. In terms of whole body oxygen delivery Messmer concluded that the optimum haematocrit was 30%.[4] As the haematocrit was decreased from 45 to 30%, while maintaining normal circulating blood volume, the reduction in viscosity was sufficient to allow for increased

blood flow such that systemic oxygen transport capacity increased to 110% of control (Figure). With further reduction in haematocrit, DO_2 declines so that, at a haematocrit of 28%, DO_2 is at or below preanaemic levels.[5] Because oxygen delivery remains relatively constant between haematocrits of 28 and 45%, there is little reason for transfusing red cells to patients with haematocrits already in this range, in order to increase oxygen delivery. Shah reported no increase in oxygen delivery when one unit of red cells was transfused to critically ill patients with pretransfusion haemoglobin concentrations of $92 \pm 3\ g \cdot L^{-1}$.[6] The administration of a second unit again did not increase measured oxygen delivery, but did result in a decreased P_{50} denoting increased haemoglobin affinity for oxygen and decreased tissue delivery. An increased systemic vascular resistance was noted and Shah suggested that this was a result of increased blood viscosity. Thus, increasing the haemoglobin concentration from 92 to 111 $g \cdot L^{-1}$ in critically ill patients increased the oxygen carrying capacity of the blood but not oxygen delivery because of the counterbalancing effects of increased blood viscosity and haemoglobin-oxygen affinity.

Physiological compensation to acute normovolaemic haemodilution

Blood at a lower haematocrit has a decreased oxygen carrying capacity. In order to compensate for this decreased oxygen carriage and to maintain oxygen delivery, tissue blood flow may be augmented either by recruiting capillaries or by increasing flow through the existing capillary network or oxygen extraction ratios may be increased. With progressive reduction in haematocrit there is an incremental increase in cardiac output which peaks at 180% of control as the haematocrit approaches 20%.[7] The enhanced cardiac output is primarily a result of increased stroke volume rather than a higher heart rate. The increased stroke volume results from both enhanced preload and decreased afterload. The augmented venous return is a result of the profound reduction in viscosity and a passive increase in blood flow in the postcapillary venules. The decrease in afterload is a result of the reduction in the viscosity component of the systemic vascular resistance.

Blood has an oxygen-carrying capacity of 1.34 ml of oxygen per gram of haemoglobin and thus, at a haemoglobin of 150 $g \cdot L^{-1}$, blood carries about 200 ml of oxygen per L. An average of 50 $ml \cdot L^{-1}$ is delivered to the tissues and the result is that mixed venous blood has an oxygen content of about 150 $ml \cdot L^{-1}$ and an oxygen saturation ($S\bar{v}O_2$) of 75%. Mixed venous oxygen saturation reflects the activity of a variety of vascular beds with some tissues (muscle, skin, viscera) extracting less oxygen and others (brain, heart) extracting proportionally more. With normovolaemic haemodilution (NVH), enhanced oxygen extraction may occur in those tissue beds which normally consume a small proportion of the available oxygen (DO_2). This increased extraction ratio (ER) will result in a lower $S\bar{v}O_2$. and reflects reduced oxygen reserves in the venous blood even though DO_2 is maintained. In the supply-dependent beds of the brain and the heart, an ER of 55–70% occurs under basal conditions.[8,9] In order to preserve oxygen consumption and aerobic metabolism in the coronary and cerebral vascular beds under conditions of NVH, capillary and coronary blood flow must increase by more than the increase in cardiac output. As the haematocrit decreases to 15%, whole body oxygen ER increases from 38% to 60% and the $S\bar{v}O_2$ decreases from 70% to 50% or less.[10] There is evidence of decreased myocardial oxygen consumption and this may be due to an impairment of myocardial oxygen extraction.[11] When DO_2 is not adequate to meet tissue metabolic requirements, even with enhanced oxygen extraction, VO_2 decreases and tissues survive by anaerobic metabolism. In animals, the onset of coronary lactate production occurs at a haematocrit below 10%.[12]

The point at which DO_2 is no longer capable of supporting cellular respiration and VO_2 declines is defined as the "critical oxygen delivery" ($DO_{2\text{-crit}}$).[9] The $DO_{2\text{-crit}}$ has been defined in animals but not yet in humans. Mortality in baboons undergoing exchange transfusion with dextran 70 is 100% at haematocrit levels of 5%.[13] Shibutani, studying coronary artery bypass patients during the prebypass period, reported that VO_2 was stable as long as DO_2 was $>330\ ml \cdot min^{-1} \cdot m^{-2}$.[14] When DO_2 was decreased below $330\ ml \cdot min^{-1} \cdot m^{-2}$, $\dot{V}O_2$ decreased proportionally. Shibutani concluded that below this critical DO_2 level, increased oxygen extraction was no longer a sufficient compensatory mechanism and that tissues suffered oxygen deprivation. Gilbert, studying patients with systemic sepsis, evaluated the effect of blood transfusion on patients with circulatory failure and haemoglobin levels below 100 $g \cdot L^{-1}$.[15] Patients were transfused from a mean haemoglobin concentration of 86 $g \cdot L^{-1}$ to 112 $g \cdot L^{-1}$. Although DO_2 was increased, VO_2 only increased in those patients who had elevated serum levels of lactic acid, before transfusion. The measured DO_2 in this group, before transfusion, was $371\ ml \cdot min^{-1} \cdot m^{-2}$ and was not adequate to sustain aerobic metabolism. Serum concentrations of lactic acid were decreased following blood transfusion. Patients without lactic acidosis had pretransfusion DO_2 of $428\ ml \cdot min^{-1} \cdot m^{-2}$ and did not demonstrate increased VO_2 following transfusion, suggesting that those levels of delivery were not metabolically limiting. Although Gilbert and Shibutani estimate a similar $DO_{2\text{-crit}}$ in humans, Astiz was unable to identify a threshold value for DO_2 in 100 patients with either sepsis or acute myocar-

dial infarction.[16] Lactic acidaemia was present in some patients despite DO_2 as high as 811 ml · min^{-1} · m^{-2} and it was concluded that this reflected the influence of distributive flow abnormalities. Finally, the mortality rate of eight patients with a mean haematocrit of 9%, who refused transfusion for religious reasons, was 87%.[17] Carson, in a similar population of patients, reported a mortality rate of 75% in patients with haematocrits of 24% or less, who lost 500–2000 ml at operation.[18] This implies that haematocrits in this range are not sufficient to maintain DO_2 necessary to support cellular respiration.

The organism may improve tissue oxygenation with rightward shift (higher P_{50}) of the oxygen dissociation curve for haemoglobin. This occurs rapidly, is achieved through increased levels of 2,3-DPG and results in increased off-loading of oxygen to tissues at any given blood O_2 tension.[19] Stored blood has decreased concentrations of 2,3-DPG and the level is inversely proportional to the age of the blood.[20] Shah has demonstrated that the administration of as little as two units of stored blood may lead to a decreased P_{50} and result in no increase in DO_2 despite an enhanced oxygen carrying capacity of the blood.[6]

The above data suggest that there are considerable physiological mechanisms which compensate for acute haemodilution and preserve tissue oxygen delivery. However, if these compensatory mechanisms are not intact, DO_2 may not be preserved and organ dysfunction may result. Older patients are less able to increase stroke volume, ejection fraction and cardiac output in response to exercise.[21] This is likely due to the heightened aortic impedance resulting in increased left ventricular afterload and a less compliant ventricle which limits left ventricular end-diastolic volume and the Starling response. In healthy, elderly patients (average age 68 yr) presenting for total hip replacement, normovolaemic haemodilution reduced the haematocrit from 41 to 28%.[22] Heart rate, blood pressure, and cardiac output were unchanged. There was a reduction in oxygen delivery as a result of the failure to compensate for the lowered oxygen carrying capacity by an increased cardiac output. Whether this reduction in oxygen carriage will be reflected in increased morbidity or mortality is not clear. Vara-Thorbeck reported that the outcome of patients with a mean age of 69 yr (range 60–82 yr), without coronary artery disease, undergoing major surgery using normovolaemic haemodilution (haematocrit 27–29%) was not different from the outcome of patients whose mean age was 46 yr (range 21–59 yr).[23] Although chronological age does not necessarily parallel physiological age and there are wide individual differences in functional capability in a population, the compensatory mechanisms that preserve DO_2 during normovolaemic haemodilution are reduced in the elderly and haemodilution should be used with caution.

Patients with coronary artery disease have a reduced capacity to increase coronary artery blood flow and perhaps cardiac output.[24] This may limit the degree of haemodilution that can be tolerated by these patients as the increased flows represent essential compensatory mechanisms for safe normovolaemic haemodilution. Geha has demonstrated that a combination of NVH to a haematocrit of 20% and a 67% stenosis of the LAD artery resulted in electrocardiographic evidence of ischaemia and deterioration of cardiac function in a dog model.[25] Crystal, in an animal model, combined a reduced perfusion pressure in an isolated LAD artery (to mimic moderate coronary insufficiency) with acute NVH to a haematocrit of 17%.[26] A reduction in myocardial oxygen consumption and systolic function (as measured by segmental shortening) was observed. It was concluded that relatively modest haemodilution may compromise ventricular metabolism and function in the presence of depleted or exhausted coronary vasodilator reserve. In dogs with critical coronary artery stenosis, impaired wall motion was observed when the haematocrit was reduced from 45 to 35%.[27] Rao electively haemodiluted patients presenting for coronary artery bypass grafting before induction of general anaesthesia to a haematocrit of 26% in an effort to reduce homologous transfusion requirements.[24] In patients with impaired left ventricular function, left ventricular end diastolic pressures of $\geq$16 mmHg, before operation, the heart rate, mean pulmonary artery pressure, wedge pressure, alveolar-arterial oxygen tension difference and intrapulmonary shunt all increased while mean arterial pressure, cardiac and stroke indices and endocardial viability ratio significantly decreased. After haemodilution, electrocardiographic evidence of ischaemia was observed in 22% of patients with preoperative impaired left ventricular function but was not seen in patients with normal left ventricular function. Owings retrospectively reviewed the records of 99 patients who presented for autologous blood donation before coronary artery bypass grafting.[28] During each donation, 450 ml of blood were collected while 500 ml of normal saline were administered into a forearm vein in the opposite arm. Electrocardiograms were not done routinely as part of the donation procedure. One patient (1%), with a pre-donation haematocrit of 40%, developed unstable angina following donation. Weisel studied patients after coronary artery bypass grafting and compared patients receiving crystalloid with those receiving blood and colloid.[29] The colloid group had a mean haematocrit of 36% and received more homologous blood products than the crystalloid group with a mean haematocrit of 27%. However, the patients in the crystalloid group had delayed recovery of myocardial oxygen and lactate extraction after surgery, demonstrating delayed myocardial metabolic recovery. There was no difference in patient morbidity or mortality between the groups, but again there was a suggestion that modest

reductions in haematocrit are not well tolerated in patients with coronary artery disease. These reports suggest that, in the presence of moderate coronary artery stenosis, flow may not increase sufficiently to offset the loss of oxygen carrying capacity caused by haemodilution and ischaemic cardiac dysfunction may result from a modest reduction in haematocrit. Patients with critical vessel stenosis or pre-existing left ventricular dysfunction may not tolerate haemodilution to any degree. Tachycardia superimposed on either of the above situations may further compromise myocardial oxygen supply.

What conclusions can be drawn from the above information with respect to recommendations for acceptable perioperative haematocrit levels? There are no detailed, prospective studies assessing morbidity and mortality related to moderate levels of anaemia (haemoglobin concentrations of 60–90 $g \cdot L^{-1}$) in general surgical populations. Some authors continue to recommend that haematocrits be maintained in the range of 30–35% perioperatively.[30] However, the above physiological data suggest that in young, healthy patients presenting for elective surgery, haematocrits of 24–27% correlating with haemoglobin values of 80–90 $g \cdot L^{-1}$ are acceptable so long as normal intravascular volume is maintained. At these levels of haemoglobin concentration, oxygen transport capacity is similar to that seen with a haemoglobin of 150 $g \cdot L^{-1}$. Others have advocated allowing the haemoglobin concentration to decrease to 60–70 $g \cdot L^{-1}$ in this population but it should be recognized that little reserve with respect to oxygen carriage and tissue oxygen delivery is maintained at these haemoglobin concentrations.[31] The expected surgical blood loss may have some role in determining the acceptable preoperative haematocrit level, higher anticipated losses necessarily calling for preoperative levels at the upper end of the acceptable range. For older patients (>60 yr), patients with systemic disease or patients with risk factors for coronary artery disease, a haematocrit of not less than 30% is recommended. This correlates with a haemoglobin concentration of not less than 100 $g \cdot L^{-1}$ and allows for supranormal blood flow rates and oxygen delivery capacity while still preserving the oxygen carrying capacity of the blood. Patients with known coronary artery disease, especially those with left ventricular dysfunction, should not be allowed to become acutely haemodiluted to haematocrits below their starting haematocrit as the incidence of myocardial ischaemia is unacceptably high.[24] However, after coronary artery bypass grafting, lower haemoglobin concentrations may be safely permitted. While these recommendations are more conservative than those proffered by others,[31] they are consistent with the information reviewed. Measurement of oxygen extraction ratios and providing blood transfusion to patients with elevated ER will result in increased $S\bar{v}O_2$ and greater blood oxygen reserves and may be useful in higher risk patients.[12,32] This recommendation is obviously limited by the requirement for mixed venous blood sampling. Finally, although it is recognized that women have both lower haematocrits and more right-shifted haemoglobin dissociation curves than men, and may tolerate lower perioperative haematocrits, there are no data that allow for separate recommendations based on the sex of the patient.[33]

Blood component therapy

The administration of blood components in the United States doubled from 1971–1980 and continued to increase into the 1980's.[34] In Canada, there has been a decrease in the number of blood recipients over the last half-decade even though the gross amount of blood transfused has remained stable at 900,000–950,000 units $\cdot yr^{-1}$.[35] This implies a smaller number of patients receiving a larger amount of blood and may be due to the introduction of new transplant and trauma programmes in many Canadian centres.[35] About two-thirds of all transfusions are given in the perioperative period (CDC-RBC).[36] Blood component transfusions were once considered to be relatively safe but, as awareness of the risks involved in transfusion increased, there has occurred a more critical evaluation of blood utilization. Using as an indication for blood transfusion a perioperative HCT <30% or blood loss >15% of the estimated blood volume, Stehling has reported that 26% of all transfusions, in an intraoperative setting, were given unnecessarily.[37] Fresh frozen plasma was inappropriately administered in 33% of the FFP transfusions reviewed when the indications were a PT or PTT more than 1.5 times control or blood replacement of greater than one blood volume. Mozes reviewed blood component transfusions in the hospital at large and found that 42% of all transfusions were inappropriate.[38] Giovanetti considered that 33% of surgical patients were overtransfused in that red cells were administered to patients with haematocrits >36% or that post-transfusion haematocrits were >36%.[39] Seventy-five per cent of the patients who received red cells in Giovanetti's review were also given FFP as a routine practice. Using similar criteria, Tartter reported that 25–28% of patients undergoing surgery for colorectal cancer received inappropriate transfusion.[40] Fish reviewed the perioperative use of FFP using, as indications for appropriate transfusion, documented coagulopathy, untoward bleeding or both.[41] Only 47% of transfusions were considered to be indicated and appropriate. The majority of patients receiving inappropriate transfusions received two units of FFP, an amount considered by most to be inadequate for correction of coagulopathy due to factor deficiency or haemodilution. Following institution of an educational program emphasizing appropriate FFP utilization, a decrease in unnecessary FFP transfusion from 53% to 22% was reported from the same institution.[42]

In recognition of the numerous developments in transfusion medicine over the last decade and in response to the concerns that blood components were not always being used appropriately, the National Institute of Health Office of Medical Applications of Research (USA) convened Consensus Development Conferences (CDC) on fresh frozen plasma (1984),[43] platelet transfusion therapy (1986)[44] and perioperative red blood cell transfusions (1988).[36] The roles of the CDCs were to review available information regarding the utilization of the blood components, to suggest guidelines for their use, and to indicate directions for research. The content of these three CDCs form the basis around which the following discussion of perioperative blood component therapy is formulated.

Fresh frozen plasma

Fresh frozen plasma is the fluid portion of the human blood that has been centrifuged, separated and frozen within six hours of donation. It contains the labile and stable components of the coagulation, fibrinolytic and complement systems; the proteins that maintain oncotic pressure; the protein factors that modulate immunity; and the carbohydrates and minerals in similar concentrations to those in the circulation. Single donor plasma, either frozen or liquid, is comparable to FFP with the exception of being relatively Factor V deficient. However, single donor plasma is no longer available in Canada, FFP being the only whole plasma product widely available. Well-defined indications for the use of FFP include documented single or multiple coagulation factor deficiencies. Fresh frozen plasma has been widely used as a volume expander and to provide prophylaxis against coagulopathy and untoward bleeding following massive transfusion and cardiopulmonary bypass.[45] The CDC-FFP concluded that there was no justification for these uses of FFP, either because no substantive evidence of efficacy for them existed or because safer, equally effective alternative therapy exists.[43]

With respect to bleeding prophylaxis, there is no evidence that the prophylactic administration of FFP decreases transfusion requirements in patients receiving multiple transfusions or in patients after cardiopulmonary bypass who do not have documented coagulation defects. Reed compared the incidence of coagulopathy in patients receiving two units of FFP for every 12 units of modified whole blood (MWB) with those patients receiving no prophylaxis.[46] The incidence of coagulopathy was 18% in both groups. Mannucci, reviewing patients receiving at least five units of blood, compared patients receiving blood only with patients receiving one unit of FFP for every three units of blood and with patients receiving two units of FFP and three units of platelet concentrates for every ten units of blood.[47] In 94% of the patients, at least one of the routine tests of coagulation was abnormal but there was no difference among the groups with respect to measured laboratory abnormalities or in the requirements for red cells. Murray studied the coagulation changes and response to therapy during packed red cell replacement of major blood loss in twelve patients presenting for elective major surgery.[48] Coagulation tests were obtained after the estimated loss of each 0.3 blood volume and before blood product replacement. Increases of the PT and PTT above control occurred in nine of the 12 patients before one blood volume was replaced but no patient had increased clinical bleeding. In four of the seven who had blood replacement of greater than one blood volume, increased clinical bleeding was observed. All four patients had platelet counts of less than $100 \times 10^9 \cdot L^{-1}$ and platelets were transfused. In two of the four patients, despite a measured increase in the platelet count, the bleeding did not resolve and fresh frozen plasma was then administered. In both these patients fibrinogen concentrations were below 750 mg $\cdot L^{-1}$ and PT and PTT were 1.5 times control values before the FFP was administered. However, Murray concluded that, if prolongation of PT and PTT in the absence of clinical bleeding had been used as the indication for the administration of FFP, nine of twelve patients would have received FFP unnecessarily before one blood volume was lost.[48]

Prophylactic administration of FFP to patients receiving massive transfusion (>1 blood volume) or administration based on abnormal laboratory tests of coagulation, in the absence of clinical evidence of untoward bleeding, is not supported by the evidence accumulated to date.[43] The incidence of abnormal tests of coagulation is high even in patients receiving as little as five units of blood.[47] However, abnormal PT and PTT values have both a poor sensitivity and poor positive predictive value as indicators for potential bleeding tendencies and although prolonged bleeding time (> 10 min) is a very sensitive predictor of increased bleeding, it has a poor specificity.[48–51]

Patients who have received 10–15 units of blood are unlikely to develop a bleeding tendency as a result of a deficiency of platelets or coagulation factors.[52] However, as transfusion requirements increase above one blood volume, it is likely that an increasing number of patients will require either platelet concentrates or FFP or both.[48] Both dilutional thrombocytopaenia and platelet function defects have been demonstrated to occur in massively transfused trauma patients.[49,53–55] The coagulopathy that develops in the massively transfused patient is multifactorial in origin and is not due to washout of the coagulant principles alone (Table I). Harke reported 36 patients who received greater than one blood volume transfusion during surgery for trauma or after sustaining major blood loss in surgery.[55] There was no simple correlation between

TABLE I Aetiological factors contributing to haemostatic defects after surgery and blood transfusion

Congenital haemostatic defects (vascular, platelet or factor-related).
Pre-existing acquired defects
– disease-related (i.e., uraemia).
– drug-related.
Dilution of haemostatic factors with massive transfusion.
Administration of artificial plasma expanders (i.e., dextran).
Tissue injury with release of tissue thromboplastin.
Shock with hypotension, acidosis or hypothermia.
Bacteraemia with sepsis.

TABLE II Indications for the administration of fresh frozen plasma (FFP)

1 Replacement of isolated factor deficiencies.
2 Reversal of coumadin effect.
3 Treatment of pathological haemorrhage in patients who have received massive transfusion (>1 blood volume).
4 Use in antithrombin III deficiency.
5 Treatment of immunodeficiencies.

Reference 43.

the amount of blood lost and replaced and the incidence of coagulopathy. However, there was a strong correlation between both the incidence and duration of hypotension and coagulopathy. The coagulopathy was characterized by abnormalities of both the plasmatic and thrombocytic systems with prolongation of the PTT, decreased serum levels of Factor V and fibrinogen, thrombocytopaenia and impaired platelet function and disseminated intravascular coagulation. Patients with no or brief periods of hypotension had no abnormalities of coagulation despite massive transfusion, whereas patients who remained hypotensive for longer than one hour had severe coagulopathy. Patients with an intermediate duration of hypotension tended to suffer less severe degrees of coagulopathy than those patients with more prolonged hypotensive episodes. Mortality was correlated with the degree of coagulopathy, being 37.5% in those patients with no coagulopathy and increasing to 85.7% in patients with severe coagulopathy. Harke concluded that patients developed coagulopathy not because of the massive transfusion but because the massive transfusion did not occur quickly enough. Ferrara reported the clinical course of 45 patients who received massive transfusion following trauma.[56] The duration of hypotension was not different in the nonsurvivors from the survivors, but the nonsurvivors were more acidotic (pH 7.04 ± 0.06 versus 7.18 ± 0.02) and more hypothermic (31 ± 1° C versus 34 ± 1° C) than the survivors. Nonsurvivors received more transfusions but developed coagulopathy despite adequate blood, plasma and platelet replacement. Ferrara concluded that avoidance or correction of hypothermia may be critical in preventing or correcting coagulopathy in the patient receiving massive transfusion. These results offer insight into the observation that, after equivalent degrees of massive transfusion, some patients demonstrate a coagulopathy and others do not.

Open heart surgery accounts for a large proportion of the FFP transfused.[45] Excessive bleeding, defined as a perioperative requirement of more than ten units of blood or postoperative chest tube drainage of ≥ 100 ml $\cdot$ hr^{-1}, occurs in 3–5% of patients, after cardiopulmonary bypass.[57] When these patients undergo reoperation, more than half exhibit inadequate surgical haemostasis. The remaining patients bleed because of acquired haemostatic defects, most commonly related to acquired platelet dysfunction.[58] Coagulation factors remain well above levels normally considered to be adequate for haemostasis, even in patients who have excessive bleeding after CPB.[57] Milam studied 75 patients who underwent open-heart surgery and CPB but who were not transfused.[59] Serum levels of factors V, VII and fibrinogen were decreased by 30–40% but no patient developed abnormal bleeding or required replacement therapy. Umlas evaluated the effect on coagulation of administering frozen deglycerolized red cells and no plasma to patients during and after CPB.[60] They found no difference in laboratory results or postoperative bleeding when compared with a control group that received stored liquid blood. Martinowitz randomized 40 post-cardiopulmonary bypass patients to receive either the plasmatic fraction of whole blood or the cellular fraction.[61] Following administration of the cellular fraction, an increase in both platelet count and function and a decrease in bleeding time was noted. No such improvement in coagulation was recorded after administration of the plasmatic fraction.

The CDC-FFP concluded that there were five indications for the administration of FFP (Table II).[43] Fresh frozen plasma is effective for treatment of deficiencies of factors II, V, VII, IX, X, XI when specific component therapy is neither available nor appropriate. Requirement for FFP varies with the specific factor being replaced and a haematologist can assist in determining appropriate transfusion requirements. To reverse the effects of coumadin in the absence of clinically untoward bleeding, two units of FFP can be administered.[31] In the bleeding, anticoagulated patient transfusion of six units of FFP has been recommended for rapid reversal of the coumadin effect.[62] Patients who have been massively transfused (>1 blood volume) and who demonstrate clinical evidence of abnormal coagulation are more likely to do so as a result of thrombocytopaenia or platelet dysfunction than coagulation factor depletion. Initial therapy should consist of platelet concentrate administration and FFP should be reserved for patients demonstrating abnormal bleeding in

TABLE III Indications for the administration of platelet concentrates

1 Clinically significant bleeding in a patient with thrombocytopaenia or a platelet function abnormality.
2 Bleeding prophylaxis in patients with severe ($\leq 20 \times 10^9 \cdot L^{-1}$) thrombocytopaenia.
3 Following massive transfusion with thrombocytopaenia and clinically abnormal bleeding.

Reference 44.

whom platelet concentrates have failed to reverse the bleeding tendencies. Transfused units of stored blood may contribute to the coagulation factor pool and a 6–8 unit transfusion of platelet concentrates contains a plasma volume equivalent to 1–1.5 units of FFP. If FFP is indicated, large volumes (600–2000 ml, 4–8 units) given rapidly are necessary to result in clinically important increases in serum levels of coagulation factors.[62]

Platelet concentrates

Platelet rich plasma is obtained following centrifugation of fresh whole blood. The supernatant is transferred into the second bag of a closed system and undergoes a second centrifugation which removes all but 50 ml of plasma and results in platelet concentrate (PC). The platelet concentrate contains 60–80% of the platelets contained in a unit of fresh whole blood. To achieve an increase in platelet count, a platelet transfusion should consist of one unit of PC for each ten kg of body mass.[44] Administration of one unit of platelet concentrate should result in an increase of $10–12 \times 10^9$ platelets L^{-1} per M^2 of body surface area. Pathological processes which involve active consumption of platelets will result in decreased therapeutic response to the platelets transfused. Single donor platelets obtained via apheresis contain the equivalent of 5–8 units of PC and reduce the donor exposure of the recipient. This has obvious benefits with respect to the likelihood of disease transmission and alloimmunization. The CDC-Platelets concluded that there were three indications for platelet transfusion (Table III).[44] These included: (1) transfusion for thrombocytopaenia in association with clinical coagulopathy as might occur in bone marrow depression resulting from chemotherapy; (2) clinical coagulopathy resulting from platelet dysfunction, either congenital or acquired as in uraemia or following cardiopulmonary bypass; or (3) following massive transfusion, for coagulopathy resulting from dilutional thrombocytopaenia or platelet dysfunction or both. Platelets should not be administered during massive transfusion in the absence of documented thrombocytopaenia and clinically abnormal bleeding. The CDC-Platelets also concluded that there was no justification for prophylactic platelet administration following cardiopulmonary bypass.

The CDC-Platelets encouraged the use of platelet counts as a guide to platelet therapy in the massively transfused patient.[44] However, in the operating theatre a decision to transfuse platelets, in the presence of massive transfusion, may have to be made on clinical grounds (i.e., clinical evidence of coagulopathy) before the results of the platelet assay are known. In addition, despite the fact that platelet counts $<100 \times 10^9 \cdot L^{-1}$ have a poor predictive value for abnormal bleeding, most patients who demonstrate coagulopathy after massive transfusion are thrombocytopaenic and have platelet counts $<100 \times 10^9 \cdot L^{-1}$.[48,49,54,63] Counts and Harrigan have demonstrated that platelet dysfunction as evidenced by prolonged bleeding times may occur in 59–86% of massively transfused patients.[49,53] Harrigan[53] reported that platelet function abnormalities were more likely to result in abnormal bleeding than thrombocytopenia and Philips[54] was unable to demonstrate a positive predictive value for low platelet count and bleeding. Whenever possible, and ideally before administration of blood components, measurement of platelet counts, PT and PTT is advisable to validate the clinical decision to transfuse.

Following replacement of one blood volume, 35–40% of the platelets remain.[44] As blood replacement continues beyond 1.5 blood volumes, the thrombocytopaenia manifests as coagulopathy.[48] The platelet count at which an individual patient demonstrates coagulopathy is variable but generally will be $<100 \times 10^9 \cdot L^{-1}$.[48,49,54,63] The platelet count cannot be predicted on the basis of the volume of blood transfused.[46] Reed evaluated 33 patients, recipients of massive transfusion, and provided an analysis of expected platelets counts assuming a simple dilution effect.[46] Patients had platelet counts well above those predicted by the analysis. The increment in platelet count achieved by concentrate administration was minor compared with the increase resulting from endogenous replacement. In the individual patient, it is the dynamic interplay between platelet number and function that determines the platelet count at which abnormal bleeding will become evident. In those patients in whom the clinical bleeding does not resolve with platelet transfusion, administration of fresh frozen plasma is the next logical step.

Perioperative red blood cell transfusion

The CDC-RBC panel concluded that the sole indication for RBC transfusion was to increase oxygen carrying capacity and that, provided normovolaemia was maintained, anaemia had no adverse effect on cardiovascular function, wound healing, infection, postoperative blood loss or patient well-being until it became profound.[36] The panel outlined directions for future research in the field of perioperative red cell transfusion (Table IV) as well as a number of alternatives to homologous red cell transfusions

TABLE IV Subjects for future research on perioperative red cell transfusion

The effect of anaemia on the rate of recovery and length of hospital stay.
The determination of the risk of transfusion-transmied infection with contemporary donor screening procedures and evaluation of new measures to identify affected donors.
The determination of immune changes induced by transfusion and their clinical consequences.
The identification of organs that are specifically at risk during acute anaemia.
The development of predictors that better define the need for perioperative transfusion.
The development of appropriate blood substitutes.
The performance of prospective controlled trials to evaluate the effects of increasing the haematocrit in anaemic patients in the perioperative period.
The evaluation and improvement of the safety and efficacy of autologous transfusion and intraoperative blood salvage procedures and the definition of criteria for selection of patients.
The development of measures for the improvement of the safety of homologous blood transfusion.
The evaluation of the risks and benefits of directed donation.

Reference 36.

TABLE V Alternatives to homologous red cell transfusion

1 Autologous transfusion programmes.
2 Intraoperative blood salvage.
3 Intraoperative haemodilution.
4 Intraoperative controlled hypotension.
5 Pharmacological approaches to reduce blood loss.
6 Recombinant erythropoietin to increase preoperative haemoglobin/autologous yield.
7 Synthetic oxygen transport media.

Reference 36.

(Table V). The following discussion will focus on the role of synthetic oxygen transport media in reducing perioperative requirements for red cells. Efforts to produce a safe and effective oxygen carrying blood substitute have proceeded along two different lines. One approach has involved the development of stroma-free haemoglobin (SFH) solutions and the other has focused on the use of perfluorochemicals (PFCs) for oxygen transport.

Stroma-free haemoglobin solutions

At present, SFH solutions are prepared from outdated human blood but recombinant technology may occupy a role in the future preparation of haemoglobin solutions. Removal of the stroma is an important step in the preparation of the haemoglobin solution as it is thought to reduce the nephrotoxicity described in early clinical (animal and human) studies. The resulting solution has a high oxygen affinity (P_{50} 12–14 mmHg), a haemoglobin concentration ([Hb]) of 60–80 $g \cdot L^{-1}$ and a plasma $t_{1/2}$ of two to four hours. The increased oxygen affinity of the solution compared with blood (P_{50} 26 mmHg) is related to the loss of the organic ligand 2,3-DPG, normally found in blood. Modification of the haemoglobin molecule by the addition of pyridoxal phosphate has resulted in the formation of a pyridoxylated haemoglobin (SFH-P) with a P_{50} of 22 mmHg.[13] The low [Hb] of the SFH-P solution (70 $g \cdot L^{-1}$) is necessary to maintain an iso-oncotic solution but does allow for rapid renal filtration and this results in a short $t_{1/2}$. Polymerization of the SFH-P molecules allows for a higher [Hb] (140 $g \cdot L^{-1}$) and a $t_{1/2}$ of 40–48 hr while maintaining an iso-oncotic solution.[44] The P_{50} of the Poly-SFH-P solution was measured at 16–20 mmHg and this compares favourably with that of stored blood (18–22 mmHg).[13] Gould described total exchange transfusion with Poly-SFH-P in six adult baboons to haematocrits below 1%.[64] The final plasma [Hb] was 97 ± 4 $g \cdot L^{-1}$. Haemodynamic variables remained at baseline values throughout the exchange transfusion to zero HCT but there was a decrease in mixed venous oxygen content and an increase in the oxygen extraction ratio.

Vlahakes has reported the haemodynamic effects and oxygen transport properties of a preparation of purified, polymerized bovine haemoglobin.[65] The preparation has a haemoglobin concentration of 110 ± 10 $g \cdot L^{-1}$ and a P_{50} of 20–23 mmHg. Bovine haemoglobin oxygen affinity is regulated by chloride ion and the concentration of chloride ion in human serum results in excellent oxygen transport properties in a stroma-free environment. Eight sheep underwent exchange transfusion with the bovine solution to final haematocrits of 2.4% and plasma haemoglobin concentrations of 61 ± 16 $g \cdot L^{-1}$. Oxygen consumption was maintained in all animals although the extraction ratio was increased from 33% at baseline to 58.4% after exchange transfusion. All animals survived for more than one month without morbidity related to the exchange transfusion or the haemoglobin solution. A brisk reticulocytosis was observed by day three after exchange and the haematocrit of all animals had returned to ≥20% by day ten without further replacement therapy.

Perfluorochemicals

Perfluorochemicals (PFCs) are hydrocarbons in which the hydrogen atoms have been replaced by fluorine and the chemicals are both stable and chemically inert.[66,67] They have a high solubility for gases and can dissolve more than 50 vol% of oxygen. Perfluorochemical liquids are immiscible in aqueous systems but, when formulated as an emulsion, are miscible in blood. The first generation PFC blood substitute Fluosol-DA 20% (FDA-20) contains 20% fluorocarbons by weight. Oxygen carried by FDA-20 is directly proportional to the oxygen tension and 100 ml of FDA-20 contains 1–2 ml of oxygen at a PaO_2 of 100 mmHg. Although not large, this amount represents about

three times the volume carried by plasma. However, Gould reported that the PFC concentration (Fluocrit) that can be achieved clinically with FDA-20 was only about 5% and that the actual amount of oxygen carried by the FDA-20 was half that of plasma.[17] In a different report, Gould compared oxygen delivery in baboons who were exchange-transfused to haematocrits below 2% with either FDA-20 or a non-polymerized SFH solution.[68] The final [Hb] in the SFHS group was $47 \pm 3\ g \cdot L^{-1}$. There was a decrease in oxygen delivery at all haematocrits. Although there was no difference in the effectiveness of the two solutions, the animals transfused with FDA-20 required an FIO_2 of 1.0 whereas the animals receiving the SFHS were maintained breathing room air. Increasing the inspired FIO_2 and thus the PaO_2 of the blood will increase the oxygen carriage of both the plasma and FDA-20 but exposes the subject to the risk of pulmonary oxygen toxicity if high FIO_2's are required for prolonged periods to maintain tissue oxygen delivery.[69] A recent assessment of FDA-20 was carried out in severely anaemic (mean [Hb] $30 \pm 4\ g \cdot L^{-1}$) surgical patients with religious objections to blood transfusions.[17] Eight patients received 40 $ml \cdot kg^{-1}$ of FDA-20 when the FIO_2 could not be reduced below 0.6 without evidence of tissue anoxia. The maximal increment in arterial oxygen content ranged from 3 to 12 $ml \cdot L^{-1}$ with a mean increment of $7 \pm 1\ ml \cdot L^{-1}$. Mean oxygen carriage by plasma was $13 \pm 1\ ml \cdot L^{-1}$, almost twice that of the FDA-20. Six of the eight patients died and one of the survivors received red cell transfusions. The investigators concluded that FDA-20 was an ineffective oxygen transport medium in the setting of life-threatening anaemia. Efforts to develop improved PFC emulsions have focused on selection of more readily emulsified PFCs of high purity and acceptable $t_{1/2}$ and preparations of emulsions with greater PFC content and thus greater oxygen carrying capacity.[70]

In addition to reducing homologous blood requirements as red cell substitutes, the PFC and SFH solutions may achieve application in support of ischaemically compromised microcirculations. The lower viscosity of the solutions compared with blood would result in improved rheological characteristics and could lead to a higher tissue flow at the same blood pressure. The improved flow may compensate for the overall reduced oxygen carrying capacity in the PFC-diluted blood. Applications of PFC solutions in both experimental models and clinical treatment of myocardial and cerebral ischaemic injury is ongoing. Preliminary results are encouraging but larger well-controlled studies are required to elucidate more clearly the role of these solutions in such situations.

Compatibilty testing

Each of the four major blood groups (A, B, AB, O) is characterized by the presence or absence of specific antigens (A, B) on the red cell membrane.[71] In the serum are antibodies (anti-A, anti-B) that are formed when the red cell membrane is devoid of the A or B antigen, respectively. The Rh(D) antigen is present (Rh positive) on the red cells of most (85%) patients but the sera of those patients lacking the Rh antigen (Rh negative) does not contain Rh antibodies unless there has been a previous exposure to the Rh antigen (i.e., pregnancy or previous blood transfusion). In order to determine the ABO group, the patient's cells are mixed with antisera (anti-A, anti-B) and the resulting pattern of agglutination identifies which antigens are on the cells. The patient's serum is added to group A and B cells and again, the presence of anti-A or anti-B in the serum will give rise to a specific pattern of agglutination. The cells are then mixed with anti-Rh serum and cells expressing the Rh antigen (Rh positive) will agglutinate. Group O blood contains red cells that express neither the A or B antigen and serum containing both anti-A and anti-B antibodies. Because much of the plasma fraction is removed from packed red cells, group O cells may be safely given to patients of other blood groups and group O has been termed the universal donor group.[72–74] Once the blood has been typed, an antibody screen is performed by incubating the patient's serum with group O cells expressing most of the common antigens found in the major blood group systems. Agglutination indicates the presence of a specific antibody which may be identified further by testing the serum against panels of phenotyped red cells. A negative antibody screen on the patient's serum indicates a low probability of a major transfusion reaction occurring if the patient is transfused with type specific blood, without a crossmatch having been performed.[75]

A crossmatch is an *in vitro* transfusion that assesses the *in vivo* compatibility of donor red cells and recipient serum. In the first phase, donor cells are mixed with recipient serum at room temperature. Gross errors in ABO typing as well as the presence in the serum of important (haemolytic) antibodies are detected. This test forms the basis for the quick spin or abbreviated crossmatch. In the abbreviated crossmatch, patient serum is mixed with a 3–4% saline suspension of washed donor erythrocytes and then centrifuged for 20 seconds. The supernatant is examined for haemolysis and the erythrocyte button is suspended and examined for agglutination. Schulman reported on 19,818 patients who were transfused on the basis of a negative antibody screen and an abbreviated crossmatch.[76] Eight patients (0.04%) had antibodies in the serum which were not detected by the quick spin and potentially capable of causing a haemolytic reaction. No patient had a symptomatic transfusion reaction although two patients may have had asymptomatic haemolysis.

The crossmatch is completed by incubating the specimens from phase I in albumin at 37° in order to detect incomplete antigens. The addition of human antiglobulin serum (Coombs) to the phase II incubated specimens detects the presence of antibodies on the donor red cells. This final phase detects antibodies capable of causing haemolytic reactions that are directed against the less common, major blood group antigens (Kell, Kidd, Duffy).

Protocols for urgent and emergency transfusion

To ensure maximum safety, donor blood should undergo complete crossmatching against the recipient's blood before being administered. However, situations arise in critical care settings which mandate blood transfusion and do not allow sufficient time (40–60 min) for the performance of a crossmatch. The use of partially crossmatched (abbreviated or quick spin crossmatch), type specific, uncrossmatched or group O blood has been recommended in these situations.[72–75,77,78] Because group O red blood cells lack A and B surface antigens, they may be given to most patients with a low risk of haemolysis. However, the serum of group O blood may contain high titres of anti-A or anti-B and may cause haemolysis of the recipient's red cells. For this reason, group O blood should be given as packed cells and not as whole blood. In order to avoid sensitization of Rh negative women of child-bearing age group O Rh negative cells should be transfused to women under the age of 40 yrs.[72–74] Otherwise group O Rh positive cells may be administered. Patients may be switched to type specific blood after the administration of up to ten units of group O blood, provided that packed cells have been used.[74] Patient serum may be screened for anti-A or anti-B titres if there are concerns about switching to type specific blood after large volumes of group O have been administered.[72] If the gravity of the situation dictates immediate blood transfusion and type specific or partially crossmatched blood is not available, group O red cells may be given.[77,78] If time permits, recipient blood may be typed and type specific, uncrossmatched blood may be given. Three per cent of patients have unexpected antibodies on serum screening, the majority of these (85%) having one antibody.[74] Gervin reported on the adminstration of 875 units of type specfic uncrossmatched blood to 160 hypovolaemic trauma patients and noted no reactions.[77] Eight per cent of the patients had been transfused in the past but, again, demonstrated no evidence of a transfusion reaction. If additional time is available for serological testing an antibody screen and an abbreviated crossmatch (quickspin) will reveal most abnormal antibodies capable of causing agglutination and haemolysis. Only 0.04% of patients will have abnormal antibodies not detected by these latter two tests and the likelihood of an important transfusion reaction is extremely low.[74]

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