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Paediatric Update

Rational use of blood products

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Abstract

Blood product transfusions can be life saving and must be considered in the supportive care of children of any age with underlying oncological or haematological problems, as well as after major surgery or after serious trauma. Paediatric transfusions are particularly challenging because life-long effects of transfusion complications are more durable and serious in children than in adults, in whom the median age at transfusion is >70 years (Tynell E, Norda R, Shanwell A, Björkman A. Long-term survival in transfusion recipients in Sweden, 1993. *Transfusion* 2001, **41**, 251–255). While the general indications for transfusions in paediatric patients are similar to adults, the threshold, volumes and infusion rates for transfusions vary with age. In this Update, we discuss current blood products, then suggest transfusion 'triggers' in major surgery and haematological and oncologic practice. Finally, future developments and new possibilities are considered.

Keywords: Children; Blood products; Transfusion; Cancer

The circulatory system delivers oxygen and nutrients, removes waste products, and is essential for the function of the immune system. The term 'haemotherapy' implies the use of fluids, blood and blood components in order to maintain an adequate intravascular volume, oxygen delivery and haemostasis. Advantages of component therapy over whole blood transfusion include more efficient and cost-effective treatment of specific clinical conditions, reduced transfusion of unnecessary components, improved preservation of components, and availability of components from one blood donation to several patients. However, storage leads to unavoidable reduction of product quality which must also be taken into account for blood components.

1. Current blood products

In many European countries blood products are classified as 'pharmaceuticals', and the trend has been towards isolation and purification of the different components. However, except for some fractionated plasma proteins, efficacy validations obligatory for pharmaceuticals have not been performed. Red blood cells (RBC), platelet concentrates and fresh frozen plasma (FFP) are the most common blood products (Table 1). Both RBC and platelet concentrates are now usually stored in additive solutions with 10–30% donor plasma. FFP and RBC are generally derived from whole blood, while platelets are produced either from whole blood or by apheresis techniques. In Europe, platelets from whole blood are mostly pooled platelets which expose a patient to four blood donors. By contrast, apheresis platelets are derived from single donors and contain at least the same yield of platelets as a pooled product. In order to reduce the number of donor exposures and the risk of septic platelet transfusion reaction [2], single donor platelets or apheresis platelets are therefore preferable for paediatric platelet concentrate transfusions.

Leucocyte-depletion, resulting in a residual total of white blood cells $<1\times10^6$ per unit, has been made mandatory in a number of countries during the past year and is now performed as an integral part of the production of most RBC and platelet concentrates prepared in Western Europe. This requirement significantly reduces transfusion reactions and immune modulation [3] caused by cytokines and leucocyte degradation products. Formation of anti-human leucocyte antigen (HLA)-antibodies and febrile transfusion reactions are

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Table 1
Important blood products [4]

Components	Volume (ml)	Composition	Leucocyte content	Dose/effect
Red blood cells (concentrate)	280 ± 80	Red blood cells in autologous plasma $\geqslant 45$ g Hb	$2.5–3 \times 10^9$	10 ml/kg body weight results in an Hb increase of 17–22 g/l
Red blood cells, leucocyte-depleted and in additive solution	≈ 300[a]	Red blood cells in additive solution with $\approx 10\%$ autologous plasma > 40 g Hb	$< 1 \times 10^6$	10 ml/kg body weight results in an Hb increase of 15–20 g/l
Platelet concentrate, leucocyte-depleted and pooled (prepared from buffycoat of four donors)	≈ 300	Platelet concentrate in additive solution with $\approx 20–30\%$ autologous plasma $\approx 300 \times 10^9$ platelets	$< 1 \times 10^6$	6×10^9 platelets/kg body weight increases platelet count by $\approx 30 \times 10^9$ platelets/l
Platelet concentrate, leucocyte-depleted and single donor (prepared by apheresis)	$\approx$ 300 ml[b]	Platelet concentrate in autologous plasma or additive solution with $\approx 20–30\%$ autologous plasma $\approx 300 \times 10^9$ platelets	$< 1 \times 10^6$	6×10^9 platelets/kg body weight increases platelet count by $\approx 30 \times 10^9$ platelets/l
Fresh frozen plasma (single donor)	250–300	Frozen within a period and to a temperature that will maintain the labile coagulation factors in a functional state	$< 1 \times 10^8$	10–20 ml/kg body weight will increase coagulation factor activity 10–30%
Solvent detergent treated plasma	200	Standardised, virus inactivated product with retained coagulation factor activity	None	10–20 ml/kg body weight will increase coagulation factor activity 10–30%

[a] Can be divided into 4–8 satellite bags (paediatric packs) by using a closed or functionally closed system.
[b] Appropriate volumes may be prepared by using a closed or functionally closed system.

also virtually eliminated. Of particular importance for paediatric transfusions is that, vis-à-vis reduction of the risk of cytomegalovirus (CMV) transmission, leucocyte filtered blood components are as effective as components from CMV-negative donors [4]. However, despite this reduction of white cell 'contamination' by leucocyte-depletion, irradiation of cellular blood products with 25 Gy is still indicated in immune compromised children (i.e. transfusions to haematopoietic stem cell transplant patients; serious immunodeficiencies and patients with Hodgkin's disease) and for 'directed' transfusions from close relatives or transfusions from HLA-compatible platelet donors.

To date, post-transfusion RBC and platelet counts have been the prime measures. Less attention has been paid to RBC and platelet function. However, in spite of product improvements such as leucocyte-depletion and additive solutions, both RBC and platelet concentrates acquire storage lesions that affect their function. During RBC storage in plasma or currently used additive solutions, intra-cellular adenosine triphosphate (ATP) and 2,3-bisphosphoglycerate (2,3-DPG) concentrations decline. The 2,3-DPG level falls to 10% within 2 weeks of storage. This compromises O_2 dissociation [5], and is the reason why RBC should be <10 days old in the transfusion of very ill patients. In addition, gradual degradation of cell surface proteins compromises O_2 dissociation [6]. Cellular flexibility (important for RBC passage through small capillaries) is compromised by a reduction of intracellular ATP concentrations. Because 2,3-DPG and ATP levels normalise about 24 h after transfusion, reduced levels mainly affect transfusions to critically ill patients because oxygen transporting capacity, but not tissue oxygenation, are improved when stored RBC are transfused [7].

Another lesion is the leakage of potassium ions from RBC. Transfusion of stored RBC may cause a transient hyperkalaemia, that reverses when intracellular potassium normalises after transfusion. Stored RBC washed prior to transfusion can therefore cause hypokalaemia. Manipulation of stored RBC (such as priming of a heart–lung machine), accentuate the loss of potassium ions, and can cause cardiac arrest. Gradual increase of the Hb concentration in plasma or additive solution during storage can compromise the micro-circulation because of the strong nitric oxide (NO)-scavenging effects of free Hb.

Thus, the general practice in paediatrics of transfusing infants with RBCs not more than 5 days old is soundly based. By the same token, transfusion of RBC stored for more than 10 days should be avoided for critically ill children. For small volume 'fill up' transfusions in neonates the risk of multiple donors may justify the use of stored 'baby packs' from a single donation.

Platelet concentrates are isolated by centrifugation both when they are prepared from whole blood or by apheresis. Centrifugation results in platelet concentrates depleted of the young and large platelets which separate with the RBC [8,9]. During storage platelet concentrates shrink due to micro vesiculation. Whether prepared from whole blood or by apheresis, centrifugation and separation induce variable activation of platelets [10–12]. Prolonged apheresis processing time can result in significantly increased platelet activation with some cell separators [12]. Some of these changes are partially reversible, but invariably progress after 2–3 days of storage [11]. Increased thrombogenicity due to the accumulation of coagulation factor V on the platelet surface probably compensates for some of the storage lesions. Optimal platelet activity is, however, probably best obtained with 2–3-day old platelet concentrates. Blood banks often prepare platelet concentrates of blood type O, because they are compatible with all ABO-groups. However, attention must be paid to anti-A and anti-B antibodies present in the platelet concentrates of blood group O donors [13], and only platelet concentrates with low titre of anti-A and anti-B should be transfused in patients with blood groups other than O.

There are large individual variations in the concentrations of different plasma proteins in single donor FFP-units. However, solvent-detergent treated (SD) plasma is a standardised product [14] prepared from pools of 60–380 l FFP (larger pools in the USA). The majority of plasma proteins retain activity within normal range levels after SD treatment [14]. In Norway, SD plasma has been the sole source of plasma since 1993, and more than 140 000 units have been transfused to neonates, children and adults as a well tolerated standardised product. Currently, licenses have been applied for 'universal' SD plasma products, which can be transfused in patients of all ABO blood groups.

With respect to fractionated plasma proteins, it is important that commercial albumin for transfusion has reduced transport capacity for Naproxen, Warfarin and Digitoxin when compared with purified Sigma albumin or albumin in SD FFP (A. Nordbö, The Norwegian Radium Hospital). This finding provides one plausible scientific explanation of the observations of the Cochrane meta-analysis in which albumin administration was shown to decrease overall survival [15]. Careful monitoring of plasma levels of certain pharmaceuticals should therefore be performed in children transfused with large amounts of albumin.

The safety of blood products has now very much improved with respect to infectious agents such as human immunodeficiency virus (HIV), hepatitis C virus (HCV), hepatitis B virus (HBV) and human T cell leukaemia virus (HTLV). Sensitive antibody detecting methods for these viruses are being gradually supplemented by nucleic acid testing, which reduces the infection risk even further. In addition, plasma proteins and SD plasma are sterile-filtered and virally inactivated. Bacterial and protozoal contamination of cellular blood products still poses a danger. The danger of bacterial contamination is of particular importance in platelet concentrates stored for >3 days and in pooled platelet concentrates [2].

2. Transfusion triggers

Modern haemotherapy is based on the principle of haemodilution and the definition of transfusion 'triggers' for different blood components. Children are more susceptible than adults to the harmful effects of hypovolaemia. Volume correction is therefore of paramount importance. In general children tolerate haemodilution well. Their Hb values are lower than in adults, except at birth. Platelet concentrations, in contrast, rise to values above adult levels after birth.

For losses of up to 40% of blood volume, electrolytes and artificial colloids are the prime choice. RBC transfusion can be restricted to cases with physiological signs of inadequate oxygenation, and is generally not indicated until $>40\%$ of blood volume has been lost. With normal platelet function and coagulation factor levels, transfusions of platelet concentrates and FFP should be considered in diffuse bleeding after one blood volume has been substituted with electrolytes, artificial colloids and RBC. Specific coagulation factor deficits are best corrected with the specific purified coagulation factors, while consumption coagulopathy can be corrected with SD plasma or FFP. The indications for albumin are disputed.

2.1. Major surgery

If possible, perioperative acute normovolaemic haemodilution should be carried out [16] and red cell salvage techniques, including postoperative collection of blood from the operation area, applied. When a large blood loss is expected, preoperative autologous blood collections can be considered. These procedures were first introduced in cardiovascular surgery [17] and reduce the requirements for allogeneic RBC considerably. Autologous blood transfusion or red cell salvage has been contraindicated in cancer surgery because of contaminating tumour cells and the risk of systemic dissemination. However, leucocyte-depletion removes cancer cells [18] and irradiation of blood prior to autotransfusion eliminates contaminating tumour cells [19]. In haemodynamically stable patients, perioperative Hb values of 60 g/l and less, are well tolerated [20]. Exceptions include neonates or children with severe cardiopulmonary disease and patients undergoing

radiotherapy, in whom Hb values of at least 100 g/l are advisable. In well-monitored haemodynamically stable patients, surgical blood loss can be bridged by intraoperative extreme haemodilution to Hb values as low as 30 g/l, if combined with hyperoxic ventilation [21]. Transfused allogeneic RBC should have a good O_2-delivering capacity (i.e. <10 days old). Platelet concentrates and/or FFP are indicated in diffuse bleeding states. Advised dosage per kg bodyweight is 6×10^9 for platelets and 10–20 ml for FFP. In case of surgical bleeding, intervention by a surgeon is mandatory.

In the few patients where diffuse bleeding is not controlled by conventional blood products, the use of fresh whole blood (irradiated) [22,23] or activated factor VII [24] should be considered. Leucocytes in fresh whole blood represent an increased risk for immunomodulation, immunisation against HLA-antigens and CMV-infection. Recent introduction of a leucocyte filter which selectively removes white blood cells, but not platelets, from fresh whole blood may solve this problem [25].

2.2. Haematology and oncology

Treatment for leukaemia and other forms of cancer has become more intensive and often leads to prolonged transfusion-requiring cytopenias. The most extreme approach is haematopoietic stem cell transplantation after myeloablative treatment, but there is often a repeated and protracted need for transfusions after intensive cytotoxic treatment courses. Good blood product quality is particularly important in order to ensure maximal *in vivo* survival (and reduced transfusion frequency) when the patient's own bone marrow function is depressed. To avoid HLA immunisation, all blood products should be leucocyte filtered.

The main products transfused are RBC and platelet concentrates. Usually, the transfusion trigger for Hb is around 80 g/l and for platelets 10×10^9/l during aplasia after cytotoxic treatment. In a child with additional severe infection, evidence of platelet consumption and after stem cell transplantation, the platelet trigger is 20×10^9/l. Any child with marrow failure and bleeding with platelets $<50\times10^9$/l should be transfused, and the need for RBC (blood volume loss $>15\%$) and specific coagulation components should be carefully evaluated. During radiation, the Hb trigger is 100 g/l since anaemia, theoretically at least, causes tumour hypoxia which, in turn, is a known cause of radiation resistance.

Granulocyte transfusions have been used in desperate cases of therapy-resistant septicaemia. The required dose of $>1\times10^{11}/m^2$ granulocytes can be achieved for small children with single apheresis donors. Introduction of donor pretreatment with i.v. dexamethasone and granulocyte-colony stimulating factor (G-CSF) significantly increases the number of harvested granulocytes. Such pretreatment is now performed on ordinary blood donors in the USA [26], but caution is still advised in the pretreatment of blood donors in Europe [4].

3. Future developments

The introduction in the next few years of microbial inactivation of cellular blood components will further reduce the risk for blood-borne infections [27]. These methods will probably eliminate the need for irradiation of cellular blood products. However, in countries with low infection risks, the potential mutagenic effects of these inactivating agents must be firmly excluded, before inactivated cellular blood components can be transfused in a paediatric setting. The increased awareness of 'storage lesions' in cellular blood components, may accelerate the introduction of more appropriate collection and storage conditions [5,28].

Oxygen-carrying colloids, either based on polymerised Hb or on Perflubron, represent interesting possibilities in extreme acute normovolaemic haemodilution or multitrauma, where normal oxygen delivering capacity can be maintained for 1–2 days in spite of RBC Hb values <35 g/l. In radiotherapy, oxygen-carrying colloids could secure efficient oxygen supply without the high red cell values and concomitant increased blood viscosity and compromised micro circulation. Sizeable phase III clinical trials have been performed [29], and files for approval are now ready for submission both in Europe and the USA. Hemopure® (polymerised bovine Hb) has recently been licensed as an oxygen therapeutic in South Africa.

Eventually, additional plasma proteins will almost certainly be replaced by recombinant products. Recombinant coagulation factors such as rFVIII and rFVIIa have already been successfully introduced, but effective, safe rFIX is still not available. Specific monoclonal immunoglobulins are currently under evaluation for the prophylaxis of RhD immunisation and in cancer therapy. For the foreseeable future, however, blood donor plasma will still be the major source for IvIgG, albumin and the less frequently used plasma proteins. It is therefore important to optimise production processes for product yield and viral safety [30]. Products with retained biological activity, such as the introduction of a commercial albumin with normal transport activity, should also have high priority.

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Commentary

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There are increasing pressures to use blood 'rationally', i.e. to give the safest, most effective product, in an appropriate dose when there is no reasonable alternative. Clinical governance concerns and increasing difficulty in recruiting adequate numbers of donors should encourage analysis of the rationale behind our current clinical practices. Where the intervention carries a real risk of inducing harm, rather than simply showing no efficacy, then the drive to question and analyse treatment policies is even greater.

As Solheim and Wesenberg point out in this issue, children are very particular transfusion recipients in that

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