Revisiting transfusion safety and alternatives to transfusion

Patrick Schoettker 1, Carlos E. Marcucci 1, Gabriele Casso 2, Catherine Heim 1

Introduction

Transfusion of blood components has been an integral part of medical care for decades and may be necessary as treatment of chronic or acute conditions. Red blood cell transfusion is the quickest way to rise haemoglobin and it has been credited with saving lives of thousands since this special day when Percy Lane Oliver, honorary secretary of the Red Cross at Camberwell, United Kingdom, received an urgent call from a nearby hospital in need of a volunteer blood donor, creating the world’s first transfusion service (www.redcross.org.uk/About-us/Who-we-are/Museum-and-archives/Historical-factsheets/Blood_transfusion, 2011).

Summary

Transfusion of blood products can be life saving when used appropriately. It carries however at the same time a potential for morbidity and mortality, depending on the patient, the product or the setting. Numerous strategies have been elaborated to minimize these risks, and in recent years, transfusion has no longer been regarded as essential for the management of a wide range of diseases. Uncomplicated surgeries in well-prepared patients can now be conducted without the use of transfusions. Questions about transfusion safety and shortage have led to extensive research on alternatives to blood transfusion, ranging from non-pharmacological to pharmacological solutions. Restrictive transfusion therapies, preoperative autologous blood donations, perioperative red cell salvage, acute normovolaemic haemodilution techniques or patient blood management are potential solutions where prothrombin complex or fibrinogen concentrates, synthetic anti-fibrinolytic agents, desmopressin, rFVIIa, or erythropoiesis stimulating agents may play a complementary pharmacologic role.
Although blood transfusions are considered to be safe, severe major complications exist. Statistics show that blood causes side effects in 10% of transfusions, and serious side effects in 1/5000 transfusions. Its routine and widespread use in clinical practice ignores the fact that blood transfusion can be viewed as an organ transplant with known complexities and risks, albeit lacking the rigorous indications of solid transplants [1].

In parallel, declining donor pools, aging populations associated to a declining birth rate, difficulties in storage or increased use due to more complex surgery, have tailored a long tradition of research and clinical management aimed at finding suitable alternatives to blood transfusion. Non-pharmacological or pharmacological approaches, exploring ways of stimulating erythropoiesis or improving oxygen transport with the help of artificial oxygen carriers or combining strategies adapted to specific patients are currently undergoing numerous trials.

The aim of this article is to review the current knowledge of safety of blood transfusion and existing alternatives.

Transfusion safety

Blood transfusions have become an ever safer clinical procedure in developed countries [2]. However, major complications still exist and hemolytic reactions [3], transfusion-related acute lung injury (TRALI) [4], bacterial contamination [5] or an increase in multi-organ failure, infections, renal dysfunction or mortality have been described in specific types of patients in relation to blood products [6] (table I). While the transmission of hepatitis and HIV by blood components is nowadays rare in developed countries, bacterial contamination is the most common residual infectious hazard. Donor screening methods, improved laboratory techniques and enhanced infectious disease testing have led to a minimization of risks for blood donors and transfusion recipients. Platelets are screened for bacteria before release to minimize risk [7], plasma derivatives have been subject to pathogen removal or inactivation treatments for many years and these technologies are increasingly applied to blood components. Nevertheless, as blood transfusion is a complex multistep process involving members of various professional groups, several risk points have been identified, including donors and recipients (table II).

This understanding has led to the development of haemovigilance, defined as surveillance procedures covering the whole transfusion chain, from collection of blood and its components to follow-up of recipients. It is intended to collect and assess information on unexpected or undesirable effects resulting from the therapeutic use of labile blood products and to prevent their occurrence or recurrence (International Haemovigilance Network [IHN] 2012, www.ihn.org.com). A survey of worldwide participants demonstrated variable development of haemovigilance schemes, hindered in many countries by lack of resources, while challenges, such as fragmented blood transfusion services, cultural fear or reporting adverse events and lack of government commitment where identified challenges.

In a further effort to report incident, and therefore increase the safety of blood transfusions, the Serious Hazards of Transfusion

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<th>Complications of transfusion and approximate frequency. Adapted from data Serious Hazards of Transfusion scheme [93]</th>
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<td><strong>Transfusion risk</strong></td>
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<th>Hotspots for errors in the transfusion process (adapted from [93])</th>
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Sheme (SHOT) group was created in the United Kingdom in 1996, allowing adverse events reporting in different categories, including incorrect blood or component transfused, acute transfusion reactions, delayed haemolytic transfusion reactions, transmission related infections or near miss events. Year on year there has been a progressive increase to nowadays an almost universal participation of all National Health Service (NHS), Trusts and Health Boards. Overall, the most common adverse incidents are caused by errors, resulting in the transfusion of an incorrect component or one that does not meet the specific requirements of the patient. On the other hand, the most common unpredictable transfusion reaction is an acute transfusion reaction (allergic, severe febrile or anaphylactic). With their annual report (www.shotuk.org) and annual symposium, changes in practice to reduce complications at the Blood Services have been triggered and resulted in several initiatives to improve training and safety related to blood product transfusion. Similar results have been demonstrated by the US Food and Drug Administration Center for Biologics Evaluation and Research in the United States (www.fds.gov/downloads/biologicsBloodVaccines/SafetyAvailability/ReportaProblem/TransfusionDonation/Fatalities). Several strategies have been developed to improve transfusion safety and guidelines for improving practice, transfusion audit programs or recommendations on safe and appropriate usage of blood are just a few of them. The number of deaths and instances of major morbidity related to transfusion has decreased and moved it into a safe zone. Nowadays, complications and “near misses” are mostly due to human errors during the transfusion process, especially in relation to failure of proper patient identification during sample collection or before blood administration. The contributory factors are similar in all areas of medical practice where humans are involved and removal of manual steps in transfusion will further improve its safety, from the introduction of automated analysers in laboratories to electronic systems across the complete transfusion process, leading to end-to-end electronic control [8].

Alternatives to blood transfusion

The detection, assessment and treatment of preoperative anaemia are important strategies to minimize allogeneic blood transfusions [9]. While anaemia is the most important risk factor for transfusion, preoperative anaemia has been independently associated with increased mortality and morbidity in patients undergoing non-cardiac surgery [10]. While the need for blood is widespread, there is a major imbalance between demand and supply of donors. Recent reports already predict a significant annual blood shortage in specific countries (Ministry of health, Labour and Welfare, Japan. Proceeding of Blood Donation Promotion Committee, Pharmaceutical Affairs and Food Sanitation Council, December 2nd 2014). This evidence, along with the previously described issues on transfusion safety, has prompted a considerable research activity to develop alternatives to blood transfusion.

Non-pharmacological alternatives to allogeneic blood transfusion

Strategies to decrease perioperative blood loss, such as surgical technique, use of autologous blood salvage, acute normovolaemic haemodilution and avoidance of coagulopathy and hypothermia are of fundamental importance.

Restrictive transfusion therapy in non-bleeding patients

Blood transfusion should not be dictated alone by low blood counts, such as a low haemoglobin (Hb) concentration, platelet count, or prolonged coagulation tests. Prospective randomized controlled trials [11-14] described that a threshold for red cell transfusion of 70–80 g/L of Hb was associated with equivalent or better clinical outcomes than thresholds of 90–100 g/L, while a Cochrane review recommends that red cell transfusion is not essential until Hb falls to 70 g/L or less (www.thecochranelibrary.com/details/collection/2116331/Avoiding-unnecessary-blood-transfusion.html). These concepts are integrated in most clinical practice guidelines and pathways aimed at improving blood utilization and patient outcomes [15]. The same restrictive transfusion strategy is recommended for patients with a history of cardiovascular disease unless the patient has an acute condition such as chest pain, heart failure, hypotension or tachycardia that does not respond to fluid resuscitation. Similarly, a platelet counts greater than 50 × 10⁹/L or an international normal ratio (INR) less than 2.0 has been shown sufficient to allow invasive procedures on patients without serious bleeding.

Preoperative autologous blood donation (PAD)

Preoperative autologous donation enjoyed a great surge in popularity in the 1980s and early 1990s with the emergence of transfusion-transmitted HIV and hepatitis C. At the peak of public concern, as many as 8.5% of RBC collected in the United States were obtained from autologous donors [16]. Since the mid 1990s, however, US autologous donation volumes have declined. The emergence of alternatives to transfusion, driven by patient blood management programs, and the demonstration of the safety of lower transfusion thresholds in a number of randomized controlled trials have further eroded the indications for preoperative autologous blood donation [11,13,14,17]. Because of improvements in donor testing, risks of HIV and hepatitis transmissions have decreased dramatically. However, studies have demonstrated that PAD still carries potential risks. Individuals who have donated autologous units are more at risk of receiving transfusions from any source, compared to those that have not, mainly due to poor timing of PAD. In addition, because only the red cell component is usually transfused and administrative costs are higher than those with allogeneic donation, the cost per unit of blood transfused is many times higher than for allogeneic transfusion [18]. The clinical
effectiveness of PAD depends on the procedure-specific likelihood that an individual will avoid allogeneic transfusion, and is balanced by adverse events occurring as a result of autologous donation. A 2001 Cochrane review identified a 68% relative reduction in allogeneic blood use while the risk of receiving any transfusion after PAD was significantly increased by 24%. Current recommendations state that PAD should be considered exclusively for patients with RBC alloantibodies necessitating rare blood in volumes unlikely to be required, those at serious psychological risk for refusal of necessary allotransfusion and possibly selected healthy individuals scheduled to undergo procedures with at least a 50% risk of requiring 3 or more units of RBCs [19,20]. There is a need for further studies on the relative effectiveness of PAD compared with aggressive preoperative anaemia management and perioperative autologous cell salvage, especially in an era of restrictive triggers for blood transfusion.

Perioperative red cell salvage

Cell salvage (CS), alternatively known as ”auto-transfusion”, is a term that covers a range of techniques that scavenge blood from operative fields or wound sites, and re-infuse the blood back into the patient. Various types of cell salvage systems exist and this technique is still extensively used in the surgical setting and can be performed during the intra- and/or postoperative periods. To remove non-cellular matter prior to reinfusion, centrifugal washing of the salvaged blood or filtering may be used, depending on the system. Its role in reducing the need for allogeneic blood transfusion remains controversial. A 2015 updated Cochrane review [21] reported that the use of CS reduced perioperative allogeneic red blood cell transfusion exposure by a relative risk of 38%. The efficacy of cell salvage in reducing the need for allogeneic red cell transfusion appeared to be greatest in the setting of orthopaedic surgery (reduced relative risk of 54% vs. 23% in cardiac surgery). In cardiac surgery, there was a further significant reduction in allogeneic red cell transfusion rates if washed cell salvage was used. In case of exposure to allogeneic blood transfusion, a relative risk reduction of 37% was observed when cell salvage was combined with another active intervention (PAD, acute normovolaemic haemodilution). Overall, there was an average saving of 0.68 units of red blood cell per patient treated with cell salvage, while the saving was 0.66 units of RBC per patient if combined with another form of active intervention. Further meta-analyses or reviews concluded that cell salvage is effective at reducing the need for allogeneic RBC transfusion, without adverse impact on clinical outcomes in orthopaedic surgery [22,23] or obstetrics [24]. However, the quality of these studies varies. Gause et al. showed that the use of intraoperative red blood cell salvage in elective lumbar fusion not only did not decrease the need for blood transfusion, but was also associated with substantially greater blood loss [25]. Rubens et al. reported that processing of cardiomyotomy blood with a CS in patients undergoing cardiac surgery resulted in an increase in postoperative bleeding and greater use of allogeneic blood [26], and Djaiani et al. showed an increased transfusion of fresh frozen plasma after processing of cardiomyotomy blood in a similar setting [27].

Although cell salvage may provide ”peace of mind”, knowing a patient’s own blood will be transfused should it be needed, cell salvage is not without risks and costs. Bacterial contamination, air embolism, nephrotoxicity or coagulation disorders have been documented and must be taken into account in assessing the transfusion strategy.

Acute normovolaemic haemodilution (ANH)

ANH consists of the withdrawal of a controlled blood volume immediately before surgery in patients that have a high haemoglobin concentration, and replacement of the volume by crystalloids or colloids. The blood is stored in citrated bags and re-infused at the end of surgery. The rationale of ANH is to reduce the loss of red blood cell mass during surgical bleeding and to provide high quality blood once surgical bleeding is controlled, with a high haematocrit, platelet count, and containing high concentrations of coagulation factors. Adequate volume replacement will allow, in most individuals, an increase in cardiac output to compensate for the drop in haemoglobin. The efficacy of ANH depends on the baseline Hb concentration, the volume of blood withdrawn, the amount of intraoperative blood loss, and the Hb concentration used as transfusion trigger. For ANH to be efficacious, the expected surgical blood loss should be more than 70% of the patients circulating volume [28]. Matot et al. [29] compared ANH with standard care in elective liver resection and demonstrated the potential of ANH in reducing the need for allogeneic transfusion. In the ANH group, only 10% of patients received allogeneic blood, compared to 36% in the control group. Intraoperative hemodynamic variables and the rate of postoperative complications were comparable between groups. Similar results were published for hepatic surgery, total hip and total knee arthroplasty and radical prostatectomy [30–33].

Yet, several meta-analysis failed to find convincing evidence of the efficacy of ANH. In a 1998 meta-analysis by Bryson et al. [34], ANH reduced neither the likelihood of transfusion nor the number of units transfused when transfusion was guided by protocols. Segal et al. [35] found only modest benefits from ANH and emphasised that the safety of the procedures is unproven. Finally, in 2015 Zhou et al. identified 36 trials involving 3819 patients. Although ANH significantly reduced the risk of allogeneic blood transfusion, they raised concerns about the true efficacy of ANH since they identified significant heterogeneity and publication bias [36].

Contraindications for ANH are anaemia, acute respiratory failure, acute anuric renal failure, active ischemic cardiac disease and known coagulopathy associated with active bleeding. The maximum volume of blood to be collected per unit is limited by the amount of anticoagulant and is usually specified on the
collection bag. The blood may be kept at room temperature for no more than 4 hours after which it should be stored at 6°C. When retransfusing the blood at the end of surgery, volume overload can be a serious risk and, although wasteful, discarding surplus blood must be considered. Although ANH has been widely studied and many authors advocate its use, its safety and efficacy remains debated. Nevertheless, ANH is a cheap procedure and when used in accordance with established recommendations in selected patients, it is likely to reduce or prevent the need for allogeneic blood products.

**Patient blood management**

Timely application of evidence-based medical and surgical concepts designed to maintain Hb concentration, optimize haemostasis and minimize blood loss in an effort to improve patient outcome has led to multidisciplinary, multimodal and individualized strategies, collectively termed patient blood management (PBM) [37,38]. Evidence supports the efficacy of these strategies in managing various patients, including those with a high risk of blood loss, anaemia and transfusion [39,40]. PBM draws on a number of key strategies, using the three-pillar approach of:

- detection and treatment of preoperative anaemia;
- reduction in perioperative red blood cell loss;
- harnessing and optimizing the patient-specific physiological reserve of anaemia.

It has been endorsed by the World Health Assembly (WHA), requesting the World Health Organization (WHO) to provide its member states with training and support of the safe, rational use if allogeneic blood transfusion and transfusion alternatives [The World Health Assembly Resolution on availability, safety and quality of blood products (WHA 63.12). www.who.int/medicines/area/quality_safety/regulation_legislation/icdra/WA-1B_quality_safety_BloodProducts.pdf]. Among the various strategies utilized in PBM, perhaps the most important is the timely detection and management of anaemia, which should never be regarded as an innocent bystander [41]. Patients at risk undergoing elective surgery should be screened for anaemia as early as possible, preferably 4 weeks ahead of surgery. If present, work-up to uncover the aetiology of anaemia must be performed and appropriate treatment provided [9,42]. Rather than allowing an anaemic patient to go into the operating theatre and be transfused to rectify the Hb value, anaemia must be viewed as a contra-indication for the elective procedure (especially if high blood loss is expected) and the procedure should be rescheduled to manage anaemia first [9]. Guidelines for allogeneic blood transfusions should be established and followed, while each unit of blood should be given only when a clear indication exists [20,43-45].

The concept of PBM may be a viable, cost-effective strategy that is beneficial for both patients, with improved clinical outcome, and for health systems, with more efficient use of finite health care resources.

**Pharmacological alternatives to allogeneic blood transfusion**

Numerous options have been tailored to decrease bleeding or to stimulate erythropoiesis. Erythropoiesis stimulating agents (ESA), single or recombinant factor concentrates, haemostatic agents (aprotinin) or parenteral iron therapy and artificial oxygen carriers have each undergone reevaluation regarding their relative benefits and risks as potential alternatives to allogeneic blood transfusions.

**Alternatives to decrease bleeding**

- **Prothrombin complex concentrates (PCC), single factor concentrates and recombinant coagulation factors**

  These are approved and routinely used in the treatment of inherited coagulation factor deficiencies. Some of these products have also been approved as hemoelastic agents in acquired coagulopathies. Guidelines from a number of medical societies on their use have been published and some recommend for example that PCC’s can be given as alternative to fresh frozen plasma (FFP) in specific situations. It is however important to fully understand their indications, and randomized controlled trials powered to evaluate their effect on outcome rather than normalization of laboratory values are still missing. Variability of content of the different preparations of PCC’s, their regulatory approval status for different countries, their lack of availability and their potential risks of thrombogenicity still raise numerous questions in their use.

- **Fibrinogen concentrate**

  Fibrinogen is a key element in both primary and secondary haemostasis. In primary haemostasis it induces platelet activation and aggregation and in secondary haemostasis it is the substrate of thrombin which cleaves the fibrinogen molecules to fibrin monomers that will eventually be polymerized to form fibrin strands that stabilise the clot. Fibrinogen is produced in the liver and its plasma concentration ranges between 1.5 and 4.0 g/L. Unlike most other coagulation factors, fibrinogen is consumed during haemostasis and is therefore the first to reach critically low plasma levels [46].

  Numerous sources of fibrinogen are available. Allogeneic plasma is probably the most widely used source of fibrinogen substitution during haemorrhage, yet it is by far not the most efficient. One unit of plasma typically contains about 400 mg of fibrinogen. Restoring fibrinogen levels in severely coagulopathic patients requires a volume of 10-20 ml/kg to be transfused which increases the risk of circulatory volume overload [47]. Cryoprecipitate obtained from thawed plasma after centrifugation is the precipitated fraction of high molecular weight proteins such as von Willebrand factor, FVIII and fibrinogen. One unit of fresh frozen plasma will produce more or less 20 ml of cryoprecipitate containing about 150 mg of fibrinogen. One adult dose is usually prepared by pooling 6–10 units, providing 1 to 1.5g of fibrinogen in 120-200 ml, making it a much more efficient source of fibrinogen than plasma. Both plasma and cryoprecipitate carry an inherent risk of transfusion-related
transmission of infectious pathogens and immunologic transfusion reactions. Fibrinogen concentrate is purified, virus inactivated, lyophilised fibrinogen, extracted from human donor plasma. It is highly efficient in the substitution of fibrinogen without sharing the risks of plasma or cryoprecipitate. After intravenous administration of 30–60 mg/Kg, plasma fibrinogen levels will increase by approximately 1 g/L [48].

Fibrinogen concentrate is more efficient in increasing plasma fibrinogen levels than cryoprecipitate and at least as efficient in securing haemostasis [49].

A recent Cochrane [50] meta-analysis warns against widespread use of fibrinogen and recommends its use to be confined to a controlled clinical setting or trial. But, when treatment of coagulopathy is guided with viscoelastic point of care tests, evidence of its efficacy in reducing the need for perioperative transfusion is accumulating. In a randomised controlled trial in complex cardiac surgery, fibrinogen concentrate administration targeting high concentrations limited postoperative bleeding and reduced allogeneic transfusion of blood products [51]. Similar results were found in major aortic and paediatric cardiac surgery [52,53]. Haas et al. showed that in paediatric craniosynostosis surgery, early administration of fibrinogen concentrate reduced blood loss and the volume of RBC transfusion.

There are only some very rare reports of thromboembolic complications following treatment with fibrinogen concentrate and none of the clinical trials investigating the efficacy of fibrinogen mentioned increased thromboembolic events, but the small numbers of patients included does not allow to draw conclusions on its safety. A post-marketing analysis of fibrinogen use between 1986 and 2013, covering more than 2.5 million grams administered, reported only 383 adverse drug reactions (i.e. 1 per 24’000 g), of these 20 were hypersensitivity reactions and 28 were possible thromboembolic events [54]. Post-marketing studies depend on spontaneous reporting of potential adverse events by physicians and are known to suffer from underreporting. The results should thus be interpreted with caution.

**Synthetic anti-fibrinolytic agents**

Reducing and/or avoiding blood loss is a key component of patient blood management. Under physiologic conditions, haemostasis is achieved through constriction of damaged vessels, formation of a platelet plug and activation of coagulation factors resulting in the formation of a stabilized fibrin clot at the site of bleeding. Parallel to this, the fibrinolytic system is activated to control clot formation and propagation and dissolve the unnecessary clots [55]. Haemostatic agents exploit these physiologic pathways to tip the balance toward forming and maintaining clots, thereby reducing bleeding. Antifibrinolytics act by inhibiting the physiologic fibrinolytic pathway that is responsible for limiting and dissolving clots.

Aprotinin is a serine protease that directly inhibits plasmin whereas lysine analogous, such as aminocaproic acid (ECA) or tranexamic acid (TXA) act through interfering with the activation of plasminogen to plasmin and its binding to fibrin clots. Until 2007, aprotinin administration was widely used in cardiac surgery to prevent hyperfibrinolysis induced by cardiopulmonary bypass machine and therefore reducing perioperative blood loss. In 2008, the BART study, a large multicenter RCT comparing efficacy of aprotinin compared to lysine analogues to reduce bleeding in high-risk cardio-surgical patients, showed a significantly increase in morbidity and mortality in the aprotinin group [56]. This serious safety concern led to aprotinin withdrawal from world markets. A recent Cochrane review of more than 250 RCTs including 25,000 patients confirmed that anti-fibrinolytic drugs administration during and after major surgery, can reduce blood loss and the need of allogeneic blood cells transfusion. TXA and ECA, in contrast to aprotinin, appeared to be free of serious adverse effects.

In the CRASH-2 trial, more than 20,000 bleeding (or at risk of) trauma patients were randomized to receive TXA vs. placebo. While not demonstrating a difference in bleeding or transfusion requirements, early treatment with TXA was associated with a risk of death of 14.5% vs. 16% [57]. This agent is now recommended as an early treatment in European guidelines for the management of major trauma-induced coagulopathy [58]. In elective orthopedic surgery, as for example during total hip arthroplasty, anti-fibrinolytic agents can reduce blood loss and need of transfusions without increasing the risk deep-vein thrombosis [59]. Perioperative liberal use of antifibrinolytics in different surgical settings is therefore increasing nowadays as a bleeding reduction strategy. More scientific evidence is still needed to clearly determine real indications, right dosage and associated risks.

**Desmopressin**

Vasopressin synthetic analogue desmopressin (DDAVP; 1-deamino-8-D-arginine vasopressin) stimulates extrarenal arginine vasopressine receptors in endothelial cells, inducing an increase of circulating levels of coagulation factor VIII, Von Willebrand factor and tissue plasminogen activator [60]. DDAVP can be administered intravenously, subcutaneously, or intranasally. Perioperative DDAVP administration before or during surgery can have a significant haemostatic effects in case of Von Willebrand disease, mild haemophilia A, liver cirrhosis, uraemia, congenital and drug-acquired platelet dysfunction [60]. Primary haemostasis impairment related to preoperative platelet dysfunction can be often improved by an intravenous infusion of 0.3 μg/kg of DDAVP therefore reducing blood transfusion requirements [61]. In the last updated European guidelines for the management of bleeding and coagulopathy following major trauma, desmopressin (0.3 μg/kg) should be administered in patients treated with platelet-inhibiting drugs or with Von Willebrand disease (Grade 2C) [58].

**Recombinant Factor VIIa (rFVIIa)**

Recombinant factor VIIa improves haemostasis by enhancing thrombin formation on activated platelets. It was approved by
the United States FDA for use in haemophilic patients with bleeding. Off-label uses have been reported in operative settings, such as trauma surgery [62–64], neurosurgery [65,66] or cardiac surgery [67,68]. A retrospective review showed that if factor VIII was administered to patients with bleeding due to a coagulopathy in medical and surgical settings, 80% had complete or partial cessation of bleeding [69]. There are however major concerns about the use of rFVIIa: thrombotic complications and its cost. The risk of thrombotic events with its approved uses is low [70], but thrombotic stroke, myocardial infarction, deep-vein thrombosis and mortality have all been reported in association with off-label use of the drug [71,72].

**Pharmacological alternatives to stimulate erythropoiesis**

Erythropoiesis stimulating agents (ESA) have been approved in patients undergoing elective surgery [73,74] and in oncology patients with chemotherapy induced anaemia, based on prospective randomized trials that demonstrated reduced alloge neic transfusion in patients receiving such therapy [75,76]. While they were first approved to increase the haemoglobin levels in patients with end-stage chronic kidney disease [77], their usage has been extended to various other groups whose haemoglobin levels are below 10 g/dL or who have symptomatic anaemia. In clinical practice nowadays, the increased risks of death and thromboembolic events should be balanced against the benefits of treatment with ESAs, considering each patient’s clinical circumstances and preferences [78].

The relationship between erythropoietin, iron and erythropoiesis and the presence of iron-restricted erythropoiesis has important implications in anaemia management. While iron deficiency may be absolute in women, children or the elderly, it may also be of functional origin or due to iron sequestration [79]. Treatment and management will be closely related to its origin. While therapeutic management may primarily focus on repletion of iron stores in cases of chronic blood loss for example, therapies, such as hepcidin antagonists may be effective for patients with inflammatory anaemia. An algorithm tailored to evaluate preoperative anaemia in patients scheduled for elective surgery has been developed by a consortium of European Societies, and is centered on an evaluation for iron-restricted erythropoiesis [9]. Numerous approved intravenous iron preparations exist [80] while the risk-benefit profile of IV iron continues to undergo evaluation. The clinical setting for which IV iron is to be used should determine which preparation is chosen. IV iron can allow up to a 5-fold erythropoietic response to significant blood loss anaemia in normal individuals. One potential limitation of IV iron therapy may be that much of the administered iron ends up in the reticuloendothelial system as storage iron, form where it is not readily available for erythropoiesis. For patients with absolute iron deficiency, 50% of IV iron is incorporated into Hb within 3–4 weeks.

**Pharmacological alternatives to improve oxygen transport**

The emphasis in the development of blood substitutes appears to have shifted from products that replace massive blood loss to fluid formulations that target specific anoxic regions, treating localized hypoxia [81]. This approach is based on the observation that a chemically modified Hb solution with a very high oxygen affinity would unload oxygen only in areas with very low tissue oxygen. Polyethylene glycol (PEG) conjugated Hb, labelled MP4, has this characteristic [82].

In some specific situations, a blood substitute, in particular a red blood cell substitute may be needed which can be stored for long periods, presents no risk of virus infections and may be administered to anyone, irrespective of blood type. This may be required as a primary measure in crisis management or to supplement blood transfusion. Since the 1980s, haemoglobin (Hb)-based O₂ carriers (HBOC) of several kinds have been evaluated, such as crosslinked Hb [83,84], polymerized Hb [85–87], and poly(ethylene glycol)-conjugated Hb (PEG-Hb) [82,88,89]. Some products have reached phase-III trials, but side effects and low efficacy have prevented their clinical use until today [90,91]. It is notable that to date no blood substitute has been developed that has shown superiority over the use of blood in clinical trials. This may suggest that so far the properties of blood are irreproducible and that the effects of transfusing blood are not fully understood. Blood transfusion focuses on increasing blood’s oxygen carrying capacity (OCC), which is assumed to be a marker of adequate organ and tissue oxygen supply. This is an elusive goal because the effects of transfusion are only partially related to the increase in OCC. The desired functional effect is the restoration of circulatory oxygen delivery capacity, which is the product of blood flow (perfusion) and OCC. It is apparent that products based on chemically modified haemoglobin have an inherent handicap; there does not appear to be a practical way to prevent the scavenging of nitric oxide (NO), which causes vasoconstriction and reduction in blood flow. This effect counteracts the significant lowering of blood viscosity and peripheral vascular resistance due to anaemia, which in itself also decreases NO bioavailability owing to the associated decrease in circulatory shear stress, which lowers the production of NO by mechanotransduction, thus limiting bioavailability of this vasodilator. Studies are still underway, trying to find the artificial oxygen carrier designed for use as a red blood cell substitute [92].

**Conclusion and synthesis**

Transfusion of blood products seems the most intuitive and quickest way to increase the level of haemoglobin and has been an advocated treatment over the years. However, its practice carries a number of risks, related to the complexity of the necessary multistep process involved in the storage, preparation and administration of the blood products, as well...
as in human factors. Strategies and guidelines have been implemented and are a fundamental part of the process of increasing the safety of transfusions. Due to these identified issues as well as the future shortage of blood products, extensive research is ongoing in order to find alternatives to blood transfusion. The quest for the “magic bullet”, capable of substituting the necessary physiological properties of the blood products, associated to a risk free solution, has as of today not yielded clinically relevant solutions. A multidisciplinary approach, centered on the individualized patient, is necessary in order to further improve patient management.

Disclosure of interest: the authors declare that they have no competing interest.

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CURRENT QUESTIONS IN TRANSFUSION MEDICINE


[84] Nagababu E, et al. Site-specific cross-linking of human and bovine hemoglobin differentially alters oxygen binding and redox side