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Abstract

Transfusion of blood components is one of the most common medical treatments, and in spite of the time that has evolved since we started to transfuse blood routinely in the 1930s, there are issues associated with its use that we are still trying to improve. Issues such as when to transfuse and adverse effects associated with the transfusion are fields where new evidence is being generated that ideally should help us to indicate when and what to transfuse to the patients. The recognition that the evidence generated in randomized control trials was not widely applied to guide the indication of the transfusion of blood components has provoked the development of initiatives that try to reduce its unnecessary usage. Those initiatives, grouped under the name of patient blood management, have represented a significant paradigm change, and a growing number of activities in this field are performed in health-care facilities around the world. This article tries to summarize the latest publications in those fields.

Introduction

What can be considered the modern era of blood transfusion started in the late 1930s, when a major boost was given to transfusion practice for the first time as a result of military conflict (the Spanish Civil War [1]); this has since been a constant in the history of transfusion medicine. It has been a long journey since then. In 2011, 107 million blood donations were collected globally, although with large discrepancies among countries: half of those blood donations were collected in the high-income countries, home to 15% of the world's population [2]. Considering the number of blood components that are prepared from every whole blood donation in high-income countries and considering that in medium- and low-income countries transfusions are still given as whole blood, we can estimate that around 160 million transfusions were given globally in 2011.

In spite of the time that has elapsed since blood transfusion's introduction and the fact that it is one of the most given therapeutics in medicine, aspects associated with its use are still lacking a clear definition and are the subject of debate. This review presents what, in the view of the authors, those issues are and presents the most recent contributions in the field. The selection of these issues has been made from objective data. That is, the topics have been selected from the articles that were recommended in Faculty of 1000 during 2013 and that we consider to represent the cutting edge of transfusion medicine.

Indication for the transfusion of blood components

We are still trying to optimize blood component utilization, and in spite of the existence of many national and international guidelines for the indication of the blood components, a wide variation in blood component utilization exists [3]. This variation in blood component usage has been particularly studied in the field of the surgery. Bennett-Guerrero *et al.* [4] performed an observational cohort study in 102,470 adult patients undergoing isolated coronary artery bypass graft (CABG) surgery during 2008 at 798 sites in the US and looked at the usage of perioperative transfusion of red blood cell (RBC) concentrates, fresh-frozen plasma (FFP) and platelets. At hospitals performing at least 100 on-pump

CABG operations (82,446 cases at 408 sites), the rates of blood transfusion ranged from 7.8% to 92.8% for RBCs, 0% to 97.5% for FFP, and 0.4% to 90.4% for platelets. Multivariable analysis revealed that three hospital characteristics combined (geographic location, academic status, and hospital CABG surgery volume) explained only 11.1% of the variation in hospital risk-adjusted RBC usage. Case mix explained 20.1% of the variation among hospitals in RBC usage, suggesting that other factors such as local practice and culture in transfusion play a major role in explaining the differences [4].

One might argue that the lack of randomized controlled trials comparing different RBC transfusion thresholds in cardiac surgery and the multiplicity of health-care practitioners participating in CABG surgery care might contribute to generate differences among physicians in the perceived benefits and risks of transfusion. However, in other fields in which evidence regarding RBC transfusion thresholds exists, variation still occurs. The FOCUS (Functional Outcomes in Cardiovascular Patients Undergoing Surgical Hip Fracture Repair) study showed that a restrictive transfusion strategy did not lead to worse mortality and morbidity outcomes compared with a liberal transfusion strategy in patients with hip fracture [5]. Chen *et al.* [6] looked at the RBC transfusion rate in total joint arthroplasties—3750 primary total knee arthroplasties and 2070 primary total hip arthroplasties—performed by 83 surgeons in a large hospital network during a 15-month period. Transfusion rate in patients following arthroplasties varied widely among surgeons: from 4.8% to 63.8% for total knee arthroplasty and from 4.3% to 86.8% for total hip arthroplasty [6].

Fortunately, new randomized controlled trials of enough power have increased the evidence available to better indicate transfusion to patients in the field of RBCs. Villanueva *et al.* [7] reported the results of a clinical trial in which they compared two thresholds for RBC transfusion (restrictive-strategy hemoglobin of below 7 g/dL versus liberal-strategy hemoglobin of below 9 g/dL) in the difficult area of severe upper gastrointestinal bleeding. They enrolled 921 patients in the study with 31% of them having cirrhosis, 444 in the restrictive-strategy group and 445 in the liberal-strategy group, with a nice balance between the two groups in the different patient characteristics. In the restrictive group, there was a significant reduction in the transfusion resources used, since 49% of the patients in the restrictive group were transfused in comparison with the 84% in the liberal group ($P < 0.001$), and the mean number of RBC units transfused was significantly lower in the restrictive group (1.5 versus 3.7, $P < 0.001$). Not only was there a reduction in the resources consumed but also the probability of survival at 6 weeks was higher in the restrictive-strategy group than in the liberal group (95% versus 91%, $P = 0.02$), and the incidence of further bleeding was lower (10% restrictive versus 16% liberal, $P = 0.01$) as was the occurrence of adverse events (40% restrictive versus 48% liberal, $P = 0.02$). The authors concluded that a restrictive transfusion strategy, as compared with a liberal one, significantly improved outcomes in patients with acute upper gastrointestinal bleeding [7].

One issue that has been a matter of debate in recent years is whether we have to use a prophylactic or therapeutic strategy when supporting patients with thrombocytopenia due to hematologic malignancy diseases or its treatment. Although most platelet transfusions currently are administered as prophylaxis to increase low platelet counts and reduce the risk of bleeding, the degree to which prophylactic platelet transfusions benefit patients with severe thrombocytopenia is unclear. A recent trial suggested that a policy of transfusing platelet concentrates only when bleeding appears was successful, although the primary endpoint of the study was a reduction in the number of platelet transfusions instead of a clinically relevant outcome such as bleeding. Actually, in the group of patients with acute myeloid leukemia, the risk of non-fatal central nervous system bleeding was increased [8]. Stanworth *et al.* [9] conducted a randomized, open-label, non-inferiority trial in 600 patients who were receiving chemotherapy or undergoing stem-cell transplantation and who had thrombocytopenia. Patients were randomly assigned to receive or not receive prophylactic platelet transfusions when morning platelet counts were less than 10×10^9/L. The primary endpoint was bleeding of World Health Organization (WHO) grade 2, 3, or 4 (i.e. bleeding generally deemed clinically significant). The authors found that bleeding events occurred in 50% of the no-prophylaxis group and in 43% of the prophylactic group, suggesting that a no-prophylaxis strategy was inferior to a prophylaxis strategy in relation to the frequency of bleeding events [9]. In other words, certain subgroups of patients do benefit from platelet prophylaxis transfusion.

In summary, wide variation exists in transfusion practice among hospitals for the same pathological condition and even among professionals in the same institution, which has been particularly studied and characterized in the field of surgery. Hopefully, the recent publication of randomized controlled clinical trials provides evidence that ideally should lead to an increase in evidence-based transfusion practice and a reduction in variability.

Transfusion-associated side effects

Hemovigilance data have shown that the most frequent reported adverse event associated with the transfusion of

blood components is transfusion administration error that in some cases may cause a fatal hemolytic reaction in the recipient [10]. However, the leading cause of death associated with transfusion is transfusion-associated acute lung injury, a complication which has been recognized in the last 10 years and for which several preventative initiatives have been undertaken [11]. In recent years, retrospective studies have identified other potential side effects of RBC transfusion that were unrecognized before. The best example of its kind, noted for its impact in the media, was the 2008 study published by Koch *et al.* [12], who reported an association between RBC storage and an increase in postoperative complications.

They performed a retrospective study in the database of patients who underwent CABG or heart-valve surgery (or both) at the Cleveland Clinic between 1998 and 2006 and had received an RBC transfusion. The authors identified a total of 6002 patients; 2872 had received 8802 units of RBCs that had been stored for 14 days or less ("newer RBCs"), and 3130 had received 10,782 units of RBCs that had been stored for more than 14 days ("older RBCs"). They found that patients who were given older RBC units had higher rates of in-hospital mortality (2.8% versus 1.7%, $P = 0.004$), intubation beyond 72 hours (9.7% versus 5.6%, $P < 0.001$), renal failure (2.7% versus 1.6%, $P = 0.003$), and sepsis or septicemia (4.0% versus 2.8%, $P = 0.01$). At 1 year, mortality was significantly less in patients given newer RBCs (7.4% versus 11.0%, $P < 0.001$). Unfortunately, like many retrospective studies, the study by Koch *et al.* [12] had some flaws that oblige us to regard its findings with caution. More evident is that the two study populations were not well balanced, and statistically significant (and potentially clinically relevant) differences were present between the two study groups in several variables. Although the authors applied multivariable statistical techniques to adjust for potential confounders, it might be that they did not completely succeed in doing so [13].

It became apparent that in spite of the study's impact in the media and the perception among the public that transfusing RBCs more than 15 days old was harmful to patients, only a randomized controlled trial of enough power would finally establish the clinical impact of transfusing stored RBCs. Fortunately, three randomized controlled trials are studying the effect of RBC storage time on clinical outcomes and are recruiting patients registered at the ClinicalTrials.gov website. Two of them are recruiting patients—Cleveland Clinic, Red Cell Storage Age Study (RECESS), and Transfusion versus Fresher red blood cell Use in intensive care (TRANSFUSE)—and one (Age of Blood Evaluation Trial, or ABLE) has been completed, and publication of the results is pending [14].

In late 2012, the results of the first randomized controlled trial studying the effect of RBC storage in infants of very low birth weight was reported (Age of Red Blood Cells in Premature Infants, or ARIPI trial) [15]. The authors aimed at determining whether transfusing RBCs stored for 7 days or less compared with usual standard decreased rates of major nosocomial infection and organ dysfunction in neonatal intensive care unit patients. The double-blind, randomized controlled trial allocated 377 premature infants with a birth weight of less than 1250 g to receive transfusion of RBCs stored for 7 days (n = 188) versus standard practice (n = 189, mean RBCs storage of 14.5 days). The results showed no differences between the two study groups regarding the primary outcome (a composite measure of major neonatal morbidities and death) or secondary outcomes of a clinically suspected infection or rate of positive cultures. The authors concluded that, in the trial, the use of fresh RBCs compared with standard blood bank practice did not improve outcomes in premature infants requiring transfusion [15].

Other adverse effects of blood component transfusion in the recipient outcomes are still under scrutiny. A long-standing debate is whether perioperative RBC transfusion has a negative impact on outcome in patients undergoing major cancer surgery [16]. Linder *et al.* [17] evaluated the association of perioperative blood transfusion (PBT) with disease recurrence and mortality following radical cystectomy. Retrospectively, they identify 2060 patients who underwent radical cystectomy at the Mayo Clinic (Rochester, MN, USA). A total of 1279 patients (62%) received PBT, but these patients were significantly older (69 versus 66 years), had a worse Eastern Cooperative Oncology Group performance status, and were more likely to have muscle-invasive tumors (56% versus 49%). The authors reported that receiving PBT was associated with significantly worse 5-year recurrence-free survival (58% versus 49%), cancer-specific survival (59% versus 72%), and overall survival (45% versus 63%). On multivariate analysis for controlling for potential confounding clinical and pathologic features, PBT remained associated with significantly increased risks of postoperative tumor recurrence. Again the retrospective character of the study and the differences observed between the two study groups make it difficult to draw definite conclusions [17]. However, the list of observational or retrospective studies suggesting poorer outcomes in the recipients of blood component transfusion is continually growing and has been registered in the F1000Prime list of recommended articles [18,19].

Patient blood management

The list of potential side effects associated with blood component transfusion and also the efforts for decreasing

health-care costs have helped to create new activity related to patients undergoing surgery and, to a lesser extent, in other medical scenarios. It has been called patient blood management (PBM) and can be defined as a multidisciplinary approach to reduce the need for blood component transfusion for those patients undergoing surgery, scheduled or not. It has been one of the biggest changes in the field of transfusion medicine and represents a paradigm change for professionals working in the field. It was identified as one of the 10 key advances in blood banking and transfusion medicine by Jeffrey McCullough, editor of *Transfusion* for 16 years [20]. The list of approaches for obtaining the goal of reducing the utilization of blood component transfusion in medical and surgical care is long. In Table 1, a non-exhaustive list of strategies for reducing RBC transfusion in a surgical scenario is shown.

One key issue that has contributed greatly to the expansion and growth of PBM programs in health-care facilities is that they have been shown to be cost-effective in many of the implemented measures, although not all of them are [21]. An indicator of the interest that exists among professionals in the field of blood banking and transfusion is that the 2013 annual meeting of the American Association of Blood Banks (AABB), held in Denver, organized a pre-meeting full-day workshop about PBM programs. The number of attendees who registered in advance required the combination of three meeting rooms at the Convention Center, but the final number of attendees was higher, so entry to the rooms was closed in the morning because maximum capacity had been reached. Another demonstration of the interest in the field is that the AABB has published the first edition of *Standards for a Patient Blood Management Program*, in March 2014 [22]. In Europe, currently PBM is widely applied as has been shown in a recently published survey carried out among centers performing elective orthopedic surgery in the Netherlands. Among the responders, 69% of departments used postoperative drainage and re-infusion, 68% used erythropoietin, 32% applied acute normovolemic hemodilution, and 31% perioperative cell saver [23].

Table 1. Potential strategies to reduce transfusion of blood components during surgery

Strategy	Tools and methods
Optimize hemoglobin before surgery	Erythropoietin Iron
Reduce blood loss during surgery	Controlled hypotension Improved surgical techniques Acute normovolemic hemodilution Systemic hemostatic agents: antifibrinolytics (tranexamic acid and epsilon aminocaproic acid) and desmopressin Topical hemostatic agents: tranexamic acid, fibrin glue, and platelet gel Control of anti-coagulation or anti-aggregation medication or both
Re-infusion of lost blood	Perioperative cell saver Postoperative drainage and re-infusion
Blood usage	Point-of-care testing Apply evidence-based red blood cell transfusion threshold

The list of publications showing the beneficial effects of PBM programs in reducing blood component utilization in several settings is long. In the experience of the authors, the introduction of tranexamic acid administration in total knee arthroplasty was associated with a reduction in the RBC transfusion of 67% of patients (54% of patients in the control group and 17.6% of the treated group received RBC transfusions). In those transfused, the mean number of RBC units transfused decreased from 2.83 to 1.89 units. Tranexamic acid administration reduced the expenditure for RBC transfusion from 148.94 to 33.87 euros per patient. No differences in thromboembolic complications between the treated group and the control group were observed [24].

Leahy *et al.* [25] recently reported the impact of introducing a PBM program in a tertiary hospital. After implementation, they observed that the mean number of RBC units per admission to the hospital declined by 26%. Among the elective admissions, transfusion rates for patients undergoing cardiothoracic surgery declined (27.5% to 12.8%), and this was the leading department in the decline of RBC usage. The use of FFP and platelets showed declines of 38% and 16%, respectively. Interestingly, the authors report that the proportion of single RBC unit use increased from 13% to 28% ($P < 0.001$) [25]. Oliver *et al.* [26] have also reported a successful implementation of a PBM program in a teaching hospital, not only on surgical grounds but also in medical indications. They performed interventions throughout the hospital, including the reorganization of the Hospital Blood Utilization Committee, the revision of the local transfusion guidelines, wide distribution among the different departments of the new guidelines by using conferences and teaching materials and specifically aiming at replacing the prevailing 2-unit transfusion dictum with a "transfuse and assess" strategy, and the creation of the Transfusion Safety Officer role. As result, in a 4-year period, the number of RBC units transfused per patient discharged was reduced by 43% through the reduction in mean number of units per transfusion (from 2 to 1.5, $P < 0.001$). Prior to implementation of the PBM program, 22% and 48% of patients received 1 or 2 units of RBCs per transfusion episode, respectively; after 4 years,

the percentages were 51% and 33%, respectively ($P < 0.0001$). The mean number of RBC units per transfusion decreased significantly for approximately 50% of the indications [26].

In summary, PBM represents an important paradigm change in the field of blood transfusion and has a significant impact on health-care economics. Now the challenge is to avoid going to the other extreme of the pendulum oscillation, which is the risk of under-transfusion [27].

Abbreviations

AABB, American Association of Blood Banks; CABG, coronary artery bypass graft; FFP, fresh-frozen plasma; PBM, patient blood management; PBT, perioperative blood transfusion; RBC, red blood cell.

Disclosures

The authors declare that they have no disclosures.

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