Modern Patient Blood Management in Arthroplasty

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Open Questions

- Which are the modern transfusion risks and disadvantages?
- How feasible is a patient blood management program in the clinical daily practice?
- How should it be treated preoperative anemia?
- When is autologous blood donation advisable?

1.1 Introduction

One of the oldest and still commonest procedures in clinical practice, allogeneic blood transfusion (ABT), is not fully supported by available evidence. In the last few decades, increasing concerns about unfavorable outcomes associated with ABT, anticipation of future insufficient blood supply, and awareness of the cost (direct and indirect) of transfusion have led to the promotion of patient blood management (PBM) as a cost-effective strategy, beneficial for patients as well as for society (Shander et al. 2010). PBM programs utilize a series of measures with a proven ability to reduce ABT and to be cost-effective. Despite that the impact of PBM on patient clinical outcomes needs to be fully defined and future studies are needed, PBM should be adopted as a new standard of care.

1.2 Background

The complex of measures undertaken with a multiprofessional and multidisciplinary approach by medical and surgical staffs, in order to perform planned surgery without transfusion and to improve patient's clinical outcomes, has been termed patient blood management. This issue, regarded as one of the ten key advances in transfusion medicine over the past 50 years, has been fully developed in the last decade, in response to the different needs that emerged at the turn of the millennium. At that time the scenario shows that allogeneic blood transfusion (ABT) is universally considered part of the standard cure in major elective surgery, but relevant variations exist in the use of blood and blood products between countries and both between and within hospitals in the same country. Even limited to lower limb arthroplasty, heterogeneity in the likelihood of transfusion is very large: a 16–85 % and a 7.5–87 % rate of transfusion, for hip and

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knee surgery, respectively, have been reported (Rosencher et al. 2003; Gombotz et al. 2007). These numbers suggest that standards of care for patients undergoing elective orthopedic surgery are poorly defined, since transfusion rate does not appear to be related to case mix, surgical technique, or anesthetic practices.

Drivers for a change in blood management are different in nature but have contributed to strongly motivate international and national authorities to approve resolutions addressed to national governments and scientific societies. In Rec (2002)11, the European Council recommends member states to arrange appropriate regulatory and advisory bodies both at the national and local levels in order to implement policies encompassing the use of alternatives to allogeneic blood transfusion and preventive strategies to reduce blood loss. In 2010, the World Health Assembly in "Resolution on availability, safety and quality of blood products" (WHA 63.12), "Bearing in mind that patient blood management means that before surgery every reasonable measure should be taken to optimize the patient's own blood volume, to minimize the patient's blood loss and to harness and optimize the patient-specific physiological tolerance of anemia following WHO's guide for optimal clinical use (three pillars of patient blood management)," urged all member states to "promote the availability of transfusion alternatives including, where appropriate, autologous transfusion and patient blood management." Thereafter, regulatory agencies and scientific societies worldwide have developed guidelines and recommendations aimed to reduce the use of allogeneic blood transfusion and also to implement PBM programs. Among others, worthy of mention, the Australian National Blood Authority is in the process of developing six comprehensive modules of a PBM guideline. In particular, Module 2 (available at http://www.blood.gov.au/pbm-module-2) regards PBM in the perioperative setting. In Italy, the national scientific society of transfusion medicine (SIMTI) has emanated a complex of comprehensive recommendations (Liumbruno et al. 2011a, b, c). Also, useful guidelines are found in Leal-Noval et al. (2013).

Historical drives for advances toward the development of PBM have been:

1. Known and unknown risks of transfusion
2. Preservation of national blood inventory
3. Constraints from escalating costs

1.2.1 Risks of Transfusion

Adverse effects to transfusion are traditionally distinguished in acute reactions, which occur in minutes to hours, and delayed, which occur within days to months. Acute reactions include acute hemolytic reactions, febrile nonhemolytic reactions, allergic reactions, transfusion-associated circulatory overload (TACO), transfusion-related acute lung injury (TRALI), and transfusion-related sepsis. Also, hyperkalemia, citrate toxicity, coagulopathy, and hypothermia may occur, especially in the case of massive transfusion. Delayed transfusion reactions include delayed hemolytic reactions, active immunization toward blood cell antigens, iron overload, transfusion-transmitted infections, autoimmunization and posttransfusion purpura, and transfusion-associated graft-versus-host disease.

All these adverse effects, among which some are mostly ascribable to human errors (acute hemolytic reactions, TACO, that are among the main causes of transfusion-associated deaths), are well known, thanks to the reports of nation-based hemovigilance systems. "Haemovigilance is required to identify and prevent occurrence or recurrence of transfusion related unwanted events, to increase the safety, efficacy and efficiency of blood transfusion, covering all activities of the transfusion chain from donor to recipient." The system should include monitoring, identification, reporting, investigation, and analysis of adverse events, near misses, and reactions related to transfusion and manufacturing (WHO, http://www.who.int/bloodsafety/haemovigilance/en). Hemovigilance carries extremely important conclusions and recommendations but entails intrinsic limits. It essentially uses an incident-reporting methodology, where underreporting is common, since adverse effects may be not recognized or not ascribed to transfusion, or due to the lack of a rigorous reporting

system. More importantly, some relevant adverse outcomes are not comprehended by an even well-established hemovigilance system but require large clinical studies for coming into light. On the basis of several observational studies and some RCTs, a causative relationship with transfusion has been shown for unfavorable outcomes, including higher mortality, more thrombotic events, organ dysfunction, infections, delayed wound healing, and increased length of hospital stay; transfusion has also been associated with cancer recurrence and insurgence of non-Hodgkin lymphoma (for comprehensive reviews, see Vamvakas and Blajchman 2009; Shander et al. 2011). A dose relationship is present, but complications can be observed after administration of minimal amounts of RBC units (Rubinstein et al. 2013).

In high-income countries, because of the currently adopted diagnostic measures for HBV, HCV, and HIV, the relative transfusion-transmitted infections have been dramatically reduced. For HBV the rate is slightly higher (around 1:200,000), because of the prolonged window period before serologic conversion and because of occult HBV infection (OBI), but further reduction is possible after the introduction of the triplex HBV/HCV/HIV NAT test in some countries (among which Italy) on the basis of HBV infection prevalence. In the last decade, west nile virus (WNV) has constituted a growing challenge for the blood bank system, forcing national authorities in North America and Europe to implement plans for either testing or referring donations, adapted on the base of national and/or local epidemiology reports. Dynamics of migrating populations and tourism are also taken into account as a possible source of infections by epidemiology control bodies, which blood management national authorities refer to. In this respect, reports of transmission through transfusion of newly emerging and reemerging infections, due to protozoan parasites (malaria, babesiosis, Chagas disease, etc.), viruses (dengue, chikungunya, influence strains, coronavirus, etc.), and prions (vCJD), are a matter of concern. Implementation of specific tests for infrequent infections is not an option for unacceptable cost/benefit ratio, and selection of donors has to be guided by up-to-date protocols.

1.2.2 Concerns About Blood Inventory

In high-income countries, ongoing demographic dynamics are characterized by what is described as the "age dependency ratio," that is, the burden of the nonworking population sustained by the working population. Operating a translation in our field, the "total transfusion dependency ratio" (TTDR; Hofmann et al. 2009) has been proposed, that is, non-donating population (aged <17 or >65 years), divided by donating population, multiplied by 100. Such index is suggestive since aged patients account for a large part of all RBC transfused (45 % for patients aged >70 years). In the recently past years, the TTDR was well less than 50 %, but a rapid climb is expected in the next 20 years, escalating over 55 % in several high-income countries (Farmer et al. 2013). In this perspective, a blood supply fulfilling even a steady request can no longer be taken for granted.

1.2.3 Escalating Costs

According to the WHO Global Database on Blood Safety, in 2011, 92 million units of blood were donated, approximately half of which in high-income countries, where direct costs of blood components have progressively increased, due to ameliorated procedures of collection, testing, and processing. When considering real costs of transfusion, a long series of activities involving material resources, technologies, and personnel both in transfusion service laboratories and in the wards (indirect costs) are to be taken into account. Through activity-based costing methodology (Shander et al. 2010), it has been calculated that on average, to transfuse a single RBC unit costs $726–1,183 in the USA and $522–611 in Europe.

This initial approach, mainly aimed to reduce the use of ABT, has evolved toward a patient-centered perspective, where PBM is established in order to ultimately ameliorate patient's clinical outcomes and experience. Still, browsing papers for this discussion, we can realize that PBM continues to be interpreted as the plain concept of

avoiding ABT. Even if reduction of ABT in the perioperative course rate remains one of the main end points and this kind of data is easily obtainable, clinical research should develop instruments in order to derive outcomes more relevant for the patient's pathway.

1.3 Focus on PBM

PBM is based on three "pillars":

1. Detection and treatment of perioperative anemia
2. Reduction of surgical blood loss and perioperative coagulopathy
3. Harnessing and optimizing physiological tolerance of anemia

1.3.1 Preoperative Anemia

In the general population, the prevalence of anemia increases with age, being reported as much as 11 and 10.2 % in men and women, respectively, aged more than 65 years (Guralnik et al. 2004). In particular, among candidates for elective orthopedic surgery, one out of three to five is expected to be anemic at preadmission (Bierbaum et al. 1999; Saleh et al. 2007; Spahn 2010). Therefore, till recently, the presence of low-grade anemia has been accepted as a matter of facts, eventually to be corrected through the liberal use of RBC concentrates. Blood components were considered safe, quickly effective, readily available, and relatively inexpensive. As a consequence, preoperative anemia is a predictive factor for perioperative transfusion and still drives a relevant consumption of blood units (Khanna et al. 2003; Shander et al. 2004; Myers et al. 2004; Gruson et al. 2009), as much as 8 % for major orthopedic hip and knee surgery, in a study conducted in north England (Wells et al. 2002).

Preoperative anemia has been independently associated with an increased risk of perioperative adverse outcomes in noncardiac surgery (Carson et al. 1996; Gruson et al. 2002; Dunne et al. 2002; Beattie et al. 2009; Wu et al. 2007; Musallam et al. 2011). Moreover, low preoperative hemoglobin concentration and high patient age are constantly associated with increased risk of transfusion; additional factors are represented by comorbidity, low body weight, complexity of surgery, and female sex (Boralessa et al. 2009; Barr et al. 2011).

1.3.2 Physiological Tolerance of Anemia

Oxygen supply is essential for aerobic metabolism, where it is employed in the process of extraction of energy from organic molecules. In multicellular, complex organisms, the atmospheric oxygen reaches the tissues by diffusing through specifically developed organs and vascular structures in a liquid system, that is, blood, from which it can diffuse in peripheral tissues. More complex organisms rely on a high-efficiency carrier for oxygen in the bloodstream, for at the atmospheric partial pressure of oxygen (21 %), the amount dissolved in the water solvent would not be sufficient for life. Therefore, in mammals, the presence of an adequate quota of oxygen in the inhaled air, anatomical and functional integrity of the lungs and its vascularization, and adequate blood flow and hemoglobin content are critical for the survival of cells. Even simple organisms have developed mechanisms for sensing reduction in oxygen delivery; in more complex organisms, oxygen sensors are multiple, existing in cells (hypoxia-inducible factor, HIF), organelle (aortic and carotid chemoreceptors), and organs (kidney). When hypoxia occurs, these mechanisms become activated, ultimately leading to the adaptive phenomena that we observe during blood loss and anemia. In acute anemia, partial pressure of oxygen in arterial blood (PaO_2) and hemoglobin-oxygen saturation (SaO_2) are maximized by means of an increased ventilation and a more efficient ventilation/perfusion matching, occurring through a NO-mediated mechanism. The cardiovascular system undergoes fundamental modifications in response to acute normovolemic anemia: through activation of the sympathetic nervous system, after stimulation of vascular chemoreceptors,

both heart rate and stroke volume are increased, the resulting cardiac output (CO) augmented up to threefold in the presence of intact adaptive mechanisms. Moreover, vasodilation occurs, determining a reduction in systemic vascular resistance. Importantly, regional differences in CO are established, through differentiated degrees of vasodilation; thus, vital organs are initially preserved, the heart and the brain receiving a higher proportion of CO. Instead, the kidney appears to have a lower margin for compensation and becomes injured earlier, insomuch as hemoglobin concentration drops below 7 g/dl, during cardiac surgery (Habib et al. 2003; Karkouti et al. 2005). Increased CO is also related to reduced blood viscosity and increased venous return, associated with vasoconstriction in the splanchnic district. The relevance of adrenergic activation as a compensative mechanism is highlighted by what has been considered a paradoxical effect of β-blockade during blood loss, that is, an increased rate of perioperative myocardial infarction (van Klei et al. 2009) and stroke (Devereaux et al. 2008), following administration of adrenergic antagonists. Another compensative mechanism for tissue hypoxia is an increased peripheral oxygen extraction, consequent to lowered hemoglobin-oxygen affinity (for increased 2,3-DPG, reduced pH, and NO-mediated events) and overall enlarged capillary bed. On the other hand, some organs reduce their oxygen demand, in front of an increase in consumption by the myocardium.

In humans, tolerance of anemia has been addressed in observational studies, involving patients for whom transfusion is not an option, for unavailability or refuse; also, experimental investigations have been carried out in voluntaries. When normovolemia is maintained, Hb concentrations as low as 5 g/dl can be tolerated without adverse systemic effects (Weiskopf et al. 1998). After noncardiac surgery, Hb levels ≤7 g/dl are associated with some morbidity, but not mortality; risk of mortality increases by a factor of 1.5, for every 1 g/dl decrement below 7 g/dl (Carson et al. 2002).

In healthy subjects at steady conditions, oxygen delivery (DO_2) meets tissue oxygen demand (VO_2), exceeding fivefold the consumption at rest. However, there are relevant intraindividual differences in oxygen consumption depending on metabolic requirement. More importantly, wide interindividual differences in anemia tolerance exist, due to impairment in ill subjects of part of the compensatory mechanisms described above. In surgery settings, comorbidity, primarily cardiovascular disease, ultimately greatly increases the rate of death in postoperatively anemic patients (Carson et al. 1996, 2002).

Perioperatively, an acute blood loss is anticipated, and medical support is aimed to maintain normovolemia and to optimize the oxygen delivery/oxygen demand ratio, in order to prevent ischemic organ injury. Possible strategies therefore include measures aimed to increase DO_2 and possibly to reduce VO_2. Since $DO_2 = CaO_2 \times CO$ (where CaO_2 is the arterial oxygen content), a feasible approach to increase CaO_2 is hyperoxic ventilation, with the aim to maximize the amount of the gas physically dissolved in plasma that can become a relevant quota available for tissue oxygenation in the presence of low Hb concentrations. To support CO, inotropic drugs are used in acute normovolemic anemia. On the other hand, a reduced oxygen demand can be obtained with neuromuscular blockade, as well as induction of anesthesia. Depth of anesthesia also affects anemia tolerance, but handling this tool is not commonly practicable (see Meier and Gombotz 2013).

Current existing guidelines covering transfusion thresholds in acutely anemic patients rely on these and a number of other observational studies, as well as randomized clinical trials. This issue will be addressed in this volume by Husted and Gentilini and Ringressi. Overall, compliance with available guidelines, compiled by scientific societies and advisory bodies (see Carson et al. 2012; Retter et al. 2013; Shander et al. 2013), is a main cornerstone of PBM programs and must be highlighted when such programs are offered.

It must be stated that benefits, effectiveness, and cost-effectiveness of complete PBM programs have been not fully proven yet. It is difficult to argue against the overall beneficial outcomes of a program encompassing several measures, all

aimed to reduce ABT, improve clinical outcomes, and reduce costs. Nevertheless, although the effects of single measures are mostly known, we cannot really anticipate the effect of a complex of measures, possibly being addictive, synergistic, or even paradoxically counteracting. Studies involving a large population are needed in order to address this question, in the form of CRTs, targeting clinically relevant outcomes, or in the form of registries collecting safety and effectiveness data on patients managed in a PBM program (Gross et al. 2013). So far, initiatives involving local institutions have demonstrated the feasibility of implementing PBM programs, achieving extremely relevant goals such as fewer transfusion administered, reduced mortality and complications, lenght of stay (LOS), readmissions, and costs (Kotzé et al. 2012; Leahy et al. 2012). A recently published study (So-Osman et al. 2014a), combining restrictive transfusion thresholds, erythropoietin administration, and/or autologous blood reinfusion, reports effectiveness (but not cost-effectiveness) of erythropoietin administration, but it shows lack of benefit for cell salvage/drain reinfusion in patients with Hb levels 10–13 g/dl.

PBM therefore is not simply a transfusion alternative, as PBM programs consider a complex of practical measures, also including alternatives to transfusion. A series of tools utilizable in PBM programs is listed in Table 1.1. Single programs do not encompass all the possible measures (indeed, some are necessarily alternative),

Table 1.1 Tools for PBM programs in elective orthopedic surgery

Preadmission	Evaluation	Detect anemia and diagnose
		Detect hemostasis defects and diagnose
		Anticipate intraoperative blood loss
		Type and screen
	Interval	Treat anemia (iron, ESAs, vitamin B12, folate)
		Optimize hemostasis (withdrawal of interfering drugs)
		PABD
Admission		
Surgery		Preoperative normovolemic hemodilution
		Physical tools (body position, tourniquet, etc.)
		Blood-saving surgical techniques
		Blood-saving anesthesiology measures, including regional anesthesia
		Normothermia
		Normotension (controlled hypotension)
		Tranexamic acid
		Pharmacological support to increase CO
		Hyperoxic ventilation
		Fibrin sealants and other topic treatments
		Transfusion guidelines
		Intraoperative cell salvage
		Limit blood drawing for tests
Postoperative period		Normothermia
		Iron ± ESA
		No drain
		Postoperative shed blood reinfusion
		Transfusion guidelines
		Pharmacological support to increase DO_2
		Hyperoxic ventilation
		Limit blood drawing for tests

but a combination of some, of which a priority has to be put on the treatment of preoperative anemia, blood-sparing surgery technique, adequate hemostasis, medical support for optimization of anemia tolerance, and adhesion to protocols concerning transfusion thresholds. The choice of the measures to be undertaken has to be done on the basis of the patient's characteristics, expected blood loss, and kind of surgery, but also it has to be driven by organizational features that can condition the patient's pathway. Even though a whole process of validation of PBM programs has not been carried out, PBM in elective surgery is to be regarded as a new standard of care, and there is no reason to delay further its implementation in our institutions.

1.4 Structure of PBM Programs

As mentioned above, PBM is a multiprofessional and multidisciplinary strategy; therefore, from a managerial standpoint, its implementation will require drawing a new pathway for patients candidate for elective orthopedic surgery, with involvement of different specialists, among which anesthetists are to play a major role. The draw should be robust, including detailed algorithms for the management of patients with different features and needs, going through the various steps (e.g., see Kotzé et al. 2012). Also, organization of continue education and controlled communication processes should be included.

1.4.1 Preoperative Management

1.4.1.1 Preoperative Assessment

In elective surgery, a preadmission assessment of patient's clinical conditions is generally performed some 30 days before surgery. Potential benefits include increased patient safety, reduced cancellation or delay of surgery, reduced LOS, and increased quality of patient experience. Pillars of preanesthesia evaluation are medical records, patient interview, and physical examination and tests, where indicated (NICE 2003; ASA 2012): major surgery schedule for adults includes a complete blood cell count and blood typing (T&S).

In a PBM program, such schedule is to be further integrated with the ultimate aim of optimizing patient's medical health prior to surgery, ultimately avoiding unnecessary transfusions. For the weight that anemia has as a prognostic factor of unfavorable outcome, its diagnosis is central to subsequent correction. Etiology is heterogeneous, and unexpected diseases such as chronic kidney failure or occult malignancy are to be considered. In these cases, referral to appropriate specialist is necessary, before planning any elective surgery. Overall, iron-restricted erythropoiesis as the most relevant abnormal condition in elderly and chronic inflammation are common in candidates for lower limb arthroplasty (Spahn 2010). Consequently, the "iron status" must be assessed, by measuring blood ferritin and TSAT, together with an inflammation index (CRP). These tests can be ordered contemporaneously to full blood cell count or later, only for anemic patients, depending on organizational constrains (Goodnough et al. 2011; Royal Cornwall Hospitals 2013).

All the collected data will lead to discriminate among three possible conditions:

- Absolute iron deficiency, due to blood loss, nutritional deficiency, or malabsorption
- Functional iron deficiency, for increased erythron iron requirements (treatment with ESAs, hemoglobinopathies, or hemolytic anemias)
- Iron sequestration, in the presence of inflammation, through a hepcidin-dependent mechanism (Weiss and Goodnough 2005)

In elderly population, also vitamin B12 and folate deficiency are relatively common (Bisbe et al. 2008; Saleh et al. 2007). We suggest to order their dosage (as a reflex test) when defects are suspected, i.e., when macrocytosis is present.

In order to minimize blood loss during surgery, the assessment of hemorrhagic risk constitutes a priority. Algorithms for scoring the risk are available (Tosetto et al. 2007; Nichols et al. 2008). Fundamental is the interview, where any personal and family history of bleeding disorders must be uncovered, as well as the use of medicaments, both prescribed or not. Besides anticoagulant or

antiplatelet drugs, agents that are able to interfere with hemostasis include NSAIDs, serotonin reuptake inhibitor antidepressants, and herbal remedies such as garlic, ginkgo biloba, ginseng, and others (Ang-Lee et al. 2001).

Preoperative evaluation must also assess a transfusion strategy, beginning with the prediction of the need for ABT. Apposite algorithms have been elaborated (Mercuriali and Inghilleri 1996; Noticewala et al. 2012; Park et al. 2013), taking into account surgical technique, procedure duration, hemostatic measures, and patient's features. On the basis of that, alternatives to transfusion are to be planned, including the use of autologous blood and/or pharmacological treatments.

For major surgery, a preadmission ABO/Rh typing should be ordered. Instead, the usefulness of a red cell antibody screening depends on patient's history (previous transfusions) and on organizational peculiarities, i.e., it is advisable if pre-transfusion tests and cross-matched blood may be not available because of time constraints, when surgery occurs shortly after admission.

1.4.1.2 Preoperative Measures

Nutritional deficiencies should be treated by proper vitamin and/or mineral medicament, besides a correct diet. Treatment of iron-restricted erythropoiesis is particularly important for the prevalence of preoperative anemia and for its unfavorable consequences. It is based on the availability of two classes of agents: iron, in oral and IV formulations, and erythropoiesis-stimulating agents (ESAs).

1.4.1.3 Iron Therapy

In brief, oral iron therapy, when tolerated, will work appropriately in most iron-deficient patients, unless an absorption defect is present. When a diagnosis is made of functional iron deficiency, iron sequestration, or mixed anemia, IV iron therapy may be necessary, particularly in the presence of a systemic inflammatory response, because of inhibition of gastrointestinal absorption caused by increased hepcidin levels. At present, IV iron is included in guidelines as a recommended pharmacological measure aimed to reduce transfusion rate (Leal-Noval et al. 2013). Several formulations are available for IV use, currently for different anemic conditions. High-molecular-weight iron dextran (HMWD) should be abandoned in favor of low-molecular-weight iron dextran (LMWD), for a lower rate of adverse reactions. Ferric gluconate and iron sucrose are formulations widely used in chronic kidney disease, but adverse effects are not rare. The recently introduced ferumoxytol does not require dilution for slow IV use, in contrast to iron sucrose and sodium ferric gluconate. Ferric carboxymaltose and iron isomaltoside, still in the course of study for some applications, are proposed, as well as ferumoxytol, for total dose infusion, that is, a slow infusion of 1–1.5 g. The European Medicines Agency's Committee for Medicinal Products for Human Use (CHMP; 2013) has emanated new recommendations to manage risk of allergic reactions with intravenous iron-containing medicines indicating that IV iron medicines are used when iron supplements given by mouth cannot be used or do not work and staff trained to evaluate and manage anaphylactic and anaphylactoid reactions must be immediately available, as well as resuscitation facilities. Moreover, the utility of test dose is underscored, and a 30-min period of observation after infusion is prescribed.

1.4.1.4 Erythropoiesis-Stimulating Agents (ESAs)

In the late 1980s, ESAs were first approved for use in chronic kidney disease patients, who mostly continue to benefit of this therapy. Later on, ESAs have also been approved for oncology patients suffering from chemotherapy-induced anemia and for patients candidate for elective surgery, even though not universally. In particular, in many European countries, ESA preoperative use is not approved, unless preoperative autologous blood donation (PABD) is scheduled. More recently, following post-approval clinical trials, targeting risk of thrombotic adverse effects of ESAs, and overall increased rate of morbidity and mortality, limits for their use have been indicated, in respect to Hb levels and an appropriate antithrombotic prophylaxis, by regulatory agencies.

Used preoperatively, ESAs are able to increase Hb levels, being the equivalent of 1 RBC unit produced by day 7 of treatment. In the course of a PABD program, 5 units can be produced with a

timing compatible with storage and use during surgery (Goodnough et al. 1992). Most effective dosage and timing of administration are debated, and diverse schedules are used. Low doses of erythropoietin (400 U/kg over a 2-week period) are sufficient to exert a significant stimulus on erythropoiesis (Sans et al. 1996). Even a single administration of erythropoietin plus iron, 1 day before surgery, has been found to be effective in reducing the need in ABT in cardiac surgery (Yoo et al. 2011). Aggressive schedules are employed in the course of a PABD program, when the RBC mass produced on a 3-week period, directly related to erythropoietin dosage, can be anticipated: RBC volume (ml per kg) = 6.34 + 0.0013*X*, where *X* equals the total units of erythropoietin administered, per kg body weight (Goodnough et al. 1994). Throughout the course of ESA treatment, iron supplementation is necessary to maximize the RBC production stimulated by ESAs.

1.4.1.5 Withdrawal of Drugs

In order to prevent severe blood loss, withdrawal of anticoagulant or antiplatelet drugs is recommended, unless critical for patient's safety. Under usual circumstances, warfarin and aspirin should be discontinued, 5 days before surgery, but at least 7 days of withdrawal are necessary for clopidogrel. Stopping aspirin and/or clopidogrel for secondary prevention should be carefully weighted case by case, after discussion with the prescribing cardiologist, but maintaining low-dose aspirin is mostly recommended (Korte et al. 2011; Royal Cornwall Hospitals 2013). Experiences of urgent orthopedic surgery in patients on antiplatelet drugs should relieve general concerns about excessive perioperative bleeding (Collinge et al. 2012; Feely et al. 2013). The BRIDGE trial, targeting bridging for anticoagulation, is still ongoing.

The use of other, nonprescribed drugs and herbal remedies possibly interfering with the hemostatic process is to be discouraged. Classical NSAIDs, because of their short half-life, usually do not raise concern of intraoperative bleeding; also, there is no indication for withdrawal of COX-2 inhibitors, provided adverse cardiac effects are taken into account. Serotonin reuptake inhibitor antidepressants have been imputed to enhance perioperative bleeding, but so far a clear evidence of increased risk of ABT is lacking; it is advisable to avoid coadministration with aspirin (Movig et al. 2003; van Haelst et al. 2010). For recommended behavior regarding perioperative use of drugs, see a list in Royal Cornwall Hospitals (2013).

1.4.1.6 Autologous Blood Donation

Preoperative autologous blood donation (PABD), consisting of collecting and storing the patient's own blood prior to surgery, has been widely practiced in different surgical settings, offered to patients as a main alternative to ABT. Indeed, PABD programs in major orthopedic surgery have caused a reduction in risk of ABT (Rosencher et al. 2003; Carless et al. 2004). Greater effectiveness is obtained when a PABD program is integrated with treatment with an ESA. Yet, the overall risk of transfusion is increased, entailing an increased risk of clerical errors as well as some kind of complication also presented by PABD (TACO, fever and chills, infections, possibly immunomodulation). These and other disadvantages (over-collection, outdating, wasting) are to be taken into account in order to evaluate PABD cost/benefit ratio. The British Committee for Standards in Hematology (2007) emanated internationally recognized guidelines that do not recommend PABD unless specific conditions are present. In particular, patients still considerable candidate for PABD are children with scoliosis, patients who refuse transfusion but would consent to PABD, bearers of rare blood groups, or who are poly-immunized. A PABD program, in combination with blood salvage, may be beneficial in bilateral TKA (Boettner et al. 2009).

1.4.2 Intraoperative Management

Normothermia should be maintained intra- and postoperatively, in order to sustain physiologic hemostasis and reduce blood loss and need for transfusion (Rajagopalan et al. 2008). For methods of fulfilling this requirement, refer to specific literature.

Acute normovolemic hemodilution, consisting of the collection of 2–4 units of whole blood exchanged with crystalloid/colloid solutions and

performed in the operating theater, immediately preceding surgery, doesn't seem beneficial in the orthopedic setting (Carless et al. 2004). It is to be considered only in combination with other blood-sparing measures in selected patients undergoing spine surgery (Shander and Rijhwani 2004).

Intraoperative cell salvage is restricted to settings concerning high risk of intraoperative bleeding. In arthroplasty, it may be considered for hip surgery in a subpopulation of patients in which an expected substantial blood loss cannot be prevented by different means.

The use of antifibrinolytic drugs (i.e., tranexamic acid) has been found to be effective in minimizing blood loss in lower limb arthroplasty, more remarkably in TKA, also proving cost-effectiveness (see Henry et al. 2011; Ker et al. 2013; Irisson et al. 2012). Concerns about its safety are not completely relieved: they would be not justified for some authors (Henry et al. 2011; Sukeik et al. 2011), whereas Australian authors solicit a post-market surveillance program (Bruce et al. 2013). Different schedules are used for administering tranexamic acid, taking into account its short half-life. In TKA, when a tourniquet is used, administration must precede its release, given the activation of fibrinolysis occurring thereafter. Tranexamic acid has also been used topically in TKA and THA, obtaining a significant reduction of postoperative blood loss, without relevant complications (Wong et al. 2010; Ishida et al. 2011; Alshryda et al. 2013a, b).

In TKA, topically applied blood components, such as fibrin sealants, have been shown to be safe and effective in reducing total blood loss and ABT rate (Liu et al. 2013). In addition, some authors (Everts et al. 2006), but not others (Diiorio et al. 2012), have also found platelet gel to be effective. As a consequence, definitive recommendations on topically applied blood components cannot at present be drawn.

1.4.3 Postoperative Management

In TKA, some 50 % of the total blood loss occurs during the postoperative period (Sehat et al. 2004). Therefore, drainage is a common practice, aimed to reduce the occurrence of wound hematomas and compression of vital structures, meanwhile permitting the application of salvage/reinfusion systems. To date, two kinds of blood salvage systems are considered safe and effective, therefore widely used, including or not washing of blood cells. About the discussion on the features and safety profiles of the two systems, see Muñoz et al. (2011).

Recently, the real efficacy of closed suction drainage has been questioned, emerging that it causes an increased need for allogeneic blood transfusion (Parker et al. 2007). Instead, the use of low-vacuum drains with salvage/reinfusion systems is associated with a reduced rate of ABT and LOS (Markar et al. 2012; Haien et al. 2013). On the other hand, the use of antifibrinolytic drugs appears to be as effective as reinfusion drains in lowering the risk of ABT (Sasanuma et al. 2011) and significantly reduces the volume of shed blood, therefore rendering useless its collection (Iwai et al. 2013; Oremus et al. 2014).

To date, randomized trials comparing low-vacuum drain/blood salvage versus no drain in TKA are still insufficient. One recent study with such a design shows that the "drain" group of patients presents a higher Hb level during a 3-day postoperative period, together with lower net blood loss (Horstmann et al. 2013). This study was not powered enough to detect significant differences in either ABT or complication rate.

It seems reasonable to argue that if postoperative drains are to be used, especially on the basis of an expected high postoperative blood loss in diverse conditions, such as in hemophilic patients (Kang et al. 2014), application of a low-vacuum salvage/reinfusion system still represents the best option in order to prevent ABT need. Cost-effectiveness is debated, as Muñoz et al. (2013) found that in TKA, postoperative blood salvage would also be cost-effective in most cases, that is, in patients presenting at surgery with Hb $\leq$15 g/dl; instead, for patients presenting with Hb >13 g/dl, any form of blood salvage would be useless and would increase costs, according to So-Osman et al. (2014b). Indeed, it is to be considered that institutions in which postsurgery strategies generally do not include drainage would afford relevant costs in case of sporadic use of postoperative

blood salvage, because of both cost of devices and skill maintenance.

The use of iron and ESAs has also been proposed as immediate postoperative treatment aimed to accelerate early recovery from postoperative anemia. More trials are needed to draw any conclusion, but the use of one of two different IV iron formulations on postoperative days of lower limb arthroplasty has been effective in reducing rate of transfusion, without incremental costs (Muñoz et al. 2014).

In conclusion, in this discussion we have focused on the philosophy of PBM and on the instruments that can be used when drawing PBM programs. Aware of difficulties that may hamper their implementation, we solicit managers of public and private institutions to actively promote projects for implementation of beneficial and cost-effective PBM pathways.

Key Points

- PBM strategy has been developed because of concerns about safety of blood transfusion, future blood supply shortage, and escalating costs.
- Presently, PBM strategy is "patient centered," aiming not only to avoid blood transfusion but also target patient clinical outcomes.
- PBM implementation requires a solid design, including algorithms for management of all kinds of patients and taking into account educational and communication issues.
- Priority must be given to the treatment of preoperative anemia, improving anemia tolerance, reduction of blood loss by means of blood-sparing surgical techniques and careful hemostasis, and adherence to protocols for administering ABT.
- Despite scarcity of evidence concerning the whole protocol of PBM, adequate rationale exists for promoting wide implementation of PBM programs. Further studies are needed in order to target relevant clinical outcomes.

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