Patient Blood Management

Effectiveness and Future Potential

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Before major surgery, 30 to 40% of patients are anemic, an important consideration that is associated with increased erythrocyte transfusions, prolonged hospital length of stay, more frequent intensive care admissions, infections, and thromboembolic events, and mortality.[1–4] Surgical bleeding contributes to anemia, increases transfusions, and independently increases mortality.[5] In addition, transfusion of allogeneic blood products is associated with increased morbidity and mortality[6] and increased costs, and allogeneic blood products are a limited resource.[6–8] Therefore, as a pragmatic solution, the concept of Patient Blood Management was developed and published in its preliminary form, first in the anesthesia literature as an editorial in Anesthesiology in 2008.[9] The authors hypothesized that "Patient Blood Management will decrease the use of allogeneic erythrocyte transfusion and its cost and adverse sequelae significantly." Currently, 12 yr later, we can conclude this is indeed the case.[10–12]

Patient Blood Management has been defined as "the timely application of evidence-based medical and surgical concepts designed to maintain hemoglobin concentration, optimize hemostasis and minimize blood loss in an effort to improve patient outcome" (https://www.sabm.org/; accessed January 13, 2020). It comprises three pillars: (1) correction of anemia with hematinic medication; (2) reduction of erythrocyte loss and (3) tolerance of anemia; and each with a number of measures that can be used across perioperative periods (table 1).

Preoperative Period

Preoperative anemia is common in patients scheduled for major surgery,[1–4] ranging from 8% in patients undergoing radical prostatectomy to 64% in gynecologic surgery.[3] As expected, the prevalence of iron deficiency (ferritin less than 30 ng/ml or ferritin less than 100 ng/ml with transferrin saturation less than 20% or C-reactive protein greater than 5 mg/l) is high in anemic patients (absolute iron deficiency, 62%).[3] Interestingly, iron deficiency was also highly prevalent (33% overall) in nonanemic patients with 60% in gynecologic surgery and 44% in colorectal cancer surgery.[3] Also in cardiac surgery, iron deficiency is frequent with approximately 50% of anemic patients and 20% of nonanemic patients having absolute iron deficiency.[3] Ferritin less than 100 ng/ml has recently been shown to be associated with a more than threefold increase in 90-day mortality irrespective of the presence or absence of anemia.[13] While several definitions of iron deficiency have been used, the most accepted one is a ferritin less than 100 ng/ml or transferrin saturation less than 20%.[14,15]

Multiple studies support the benefits of treating preoperative anemia. In orthopedic surgery, treatment with intravenous iron and subcutaneous erythropoietin 1 to 3 days before surgery was associated with a reduction of erythrocyte transfusion rate from 37 to 24%, nosocomial infections from 12 to 8%, and hospital stay from 11.7 to 10.7 days. In patients with hip fractures, this treatment was associated with a decrease in mortality from 9.4 to 4.8%.[16] This reduction in infection rate is in contrast to an increase of infectious complications due to intravenous iron treatment described in an older meta-analysis.[17] However, in this meta-analysis only 11 of 75 included studies were from surgery.[17] A 21% reduction of postoperative infections was also found in a study in 605,000 surgical patients,[10] as well as in a recent meta-analysis (−9%).[11] In a prospective randomized study in patients undergoing gastrointestinal surgery with preoperative iron deficiency anemia (ferritin less than 300 ng/ml, transferrin saturation less than 25%, hemoglobin less than 12.0 g/dl for women, and less than 13.0 g/dl for men), it was shown that intravenous iron treatment approximately 10 days before surgery reduced erythrocyte transfusions and was associated with a shortened length of hospital stay from 9 to 6 days.[18] Among anemic or iron-deficient patients (ferritin less than 100 ng/ml) undergoing cardiac surgery, it was recently shown in a prospective randomized, double-blind study that combination treatment with intravenous iron, subcutaneous erythropoietin, vitamin B12, and oral folic acid 1 day before surgery reduced erythrocyte transfusions from a median of 1 to 0 units with similar secondary clinical outcomes in both groups.[19] Interestingly, there are no studies describing anemia or iron deficiency

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Table 1. Suggested Approach to Perioperative Patient Blood Management

	Elective			Emergency
	Period			
	Preoperative	Intraoperative	Postoperative	
Correct anemia and iron deficiency				
Iron (IV) + EPO + vitamin B12 + folic acid (see table 2)				
Reduce perioperative erythrocyte loss				
Improved surgical technique				
Cell salvage and re-transfusion				
Acute normovolemic hemodilution				
Avoiding coagulopathy				
Monitoring of coagulation				
Individualized and goal-directed coagulation algorithm				
Antifibrinolytics				
Fibrinogen				
PCC				
Factor XIII				
Low CVP, no hypertension, normothermia				
Reduced blood draws for laboratory testing				
Tolerance of anemia				
Tolerate low hemoglobin values (restrictive TT)				
Optimazation of hemodynamics and oxygenation				

Blue refers to elective surgery, orange to emergency surgery. Dark colors indicate application to all patients (without specific contraindications) and bright colors indicate application to some patient groups.

CVP, central venous pressure; EPO, erythropoietin; IV, intravenous; PCC, prothrombin complex concentrate; TT, transfusion trigger.

treatment specifically before gynecologic surgery. However, we expect that also on gynecologic surgery preoperative treatment of anemia and iron deficiency is beneficial.

Although late anemia treatment can be successful, early (2 to 3 weeks before surgery) detection of anemia and iron deficiency is important for ideal preoperative correction. A group of experts supports this strongly based on their exhaustive literature research for evidence-based recommendation for Patient Blood Management.[20] Also others recommend not proceeding with elective surgery in patients with correctable anemia until appropriately treated.[21] This is particularly important in patients scheduled for operations associated with a perioperative erythrocyte transfusion rate of greater than or equal to 10% or an expected blood loss of greater than or equal to 500 ml.[3,22] This analysis needs to be done by each hospital to define their own higher-risk procedures. Then, surgeons and anesthesiologists need to decide which specialty is responsible for preoperative anemia and iron deficiency detection and treatment. Obviously, it is the surgeon's task to schedule a major operation, including the date of the operation, 2 to 3 weeks in advance whenever possible. Also, measuring hemoglobin and iron parameters (ferritin and transferrin saturation)[14] at the time of decision making for major surgery can be done in the most efficacious way at the surgeon's consultation. Alternatively, referring physicians may measure hemoglobin and iron parameters already at their consultation, and refer patients to the hospital with these parameters measured. In any case, task assignment and responsibility need to be clearly defined. Finally, monitoring and feedback of the agreed upon processes is key for efficacious implementation.

An algorithm regarding preoperative anemia and iron deficiency testing and treatment needs to be defined. A potential algorithm is depicted in table 2. A group of experts[20] only assign a conditional recommendation for preoperative iron supplementation in patients with iron deficiency anemia, despite the fact that their own analysis yielded a risk reduction for the number of erythrocyte transfusions to 0.47 (0.28 to 0.79; $P = 0.005$). They assigned a conditional recommendation against the routine use of erythropoietin in preoperatively anemic patients, despite a significant reduction of erythrocyte transfusions due to potential thromboembolic events which did not achieve statistical significance in their analysis. Indeed, erythropoietin should not be used routinely, but based on an individual risk–benefit analysis. Patients with severe cerebrovascular disease and history of recent severe thromboembolic events should not be treated with erythropoietin. Nevertheless, in patients with renal anemia or anemia of inflammation, a combination treatment with intravenous iron and erythropoietin has clearly been recommended[15] and was found to be efficacious in a recent prospective randomized trial without increased thromboembolic events.[19] The lower the preoperative hemoglobin and the shorter the time to surgery is, the more liberally erythropoietin may be used. In

Table 2. Anemia Management Algorithm of the University Hospital of Zurich, Switzerland

Condition						
Hb*	Ferritin		TSAT	CCL	CRP	Treatment
Hb < 130 g/l	< 100 ng/ml	or	< 20%	≥ 50 ml/min		IV iron: 20 mg/kg†‡ SC vitamin B12: 1 mg§ PO folic acid: 5 mg‖
Hb < 130 g/l	≥ 100 ng/ml	and	≥ 20%	< 50 ml/min		SC epoetin alpha 600 U/kg BW# IV iron: 20 mg/kg† SC vitamin B12: 1 mg§ PO folic acid: 5 mg‖
Hb < 130 g/l	≥ 100 ng/ml	and	≥ 20%		> 5 mg/l	SC epoetin alpha 600 U/kg BW# IV iron: 20 mg/kg† SC vitamin B12: 1 mg§ PO folic acid: 5 mg‖
Hb ≥ 130 g/l	< 100 ng/ml	or	< 20%			IV iron 20 mg/kg†

*Applies to women and men. †With some IV iron preparations maximum dose limitations need to be respected. ‡If time to surgery is less than or equal to 5 days, add SC epoetin alpha 600 U/kg BW. §Indicates some vitamin B12 formulations may be administered intramuscularly. ‖Indicates until day of surgery. #Usually, total dose is limited to 40,000 U.

BW, body weight; CCL, creatinine clearance; CRP, C-reactive protein; Hb, hemoglobin; IV, intravenous; PO, by mouth; SC, subcutaneous; TSAT, transferrin saturation.

any case, a hemoglobin greater than 130 g/l is the target and hemoglobin concentrations greater than 150 g/l need to be avoided.

In various countries, the site of treatment differs significantly. In some countries, these treatments are administered in the hospital, while in others, the referring general practitioner may treat the patient at their consultation. Also, insurance coverage for anemia treatment is likely variable worldwide. In most countries, intravenous iron treatment is covered preoperatively in patients with a documented iron deficiency. The situation regarding erythropoietin is somewhat more diverse. In most countries, erythropoietin is reimbursed in patients with renal insufficiency and renal anemia. With other types of anemia, the situation is less uniform. In the Netherlands, erythropoietin is reimbursed if indicated for the treatment of preoperative anemia; in many other countries this is not the case. However, hospitals always have the option to cover the costs for erythropoietin to treat preoperative anemia and, given the savings in transfusion-related morbidity, it makes institutional investment in such programs well founded.[10]

Another important aspect is the perioperative management of patients receiving preoperative anticoagulation (vitamin K antagonists and direct oral anticoagulants) or dual platelet inhibition. There are several recommendations regarding the perioperative management of patients with oral anticoagulation. Based on the anticoagulant pharmacokinetics and the planned surgery bleeding risk, standard times have been proposed for when to stop the anticoagulant.[23] Such interruption times need to be longer in patients with renal or hepatic insufficiency, or other concomitant medications that interfere with anticoagulant drug metabolism.[24,25] In addition, measuring plasma levels may help guide patient management.[26] This was initially proposed mainly for emergency cases[26]; however, since rivaroxaban plasma levels of greater than 100 ng/ml have recently been associated with a greater erythrocyte loss,[27] measuring plasma levels may also be indicated in nonemergent surgery, particularly in patients at risk of having higher than expected plasma levels such as those with compromised renal function, very advanced age, comedication with amiodarone, and unknown time of last ingestion.[24] If indeed plasma levels of greater than 100 ng/ml are found, postponing surgery with a high bleeding risk may be justified. Anticoagulation bridging for most patients is not recommended because heparin bridging does not prevent thromboembolic complications and results in more perioperative bleeding.[28–30]

The 2016 American College of Cardiology/American Heart Association guidelines for the perioperative management of patients with coronary stents and dual platelet inhibition recommends delaying elective noncardiac surgery for 30 days after bare metal stent implantation and, optimally 6 months after drug eluting stent implantation. If surgery mandates P2Y12 platelet inhibitor discontinuation, aspirin is recommended to be continued and the P2Y12 platelet inhibitors restarted as soon as possible after surgery. Between 3 and 6 months after drug eluting stent implantation, surgery requiring P2Y12 platelet inhibitor discontinuation can be performed if the risk of delaying surgery further is greater than the expected risk of stent thrombosis.[31] An observational study found a high incidence of major adverse cardiac events of 20%, with a maximum in the first 42 days after stenting despite the fact that 69% of patients used aspirin until 3 days of surgery.[32] Since the majority of coronary events were non-ST elevation myocardial infarctions, a supply–demand imbalance might have occurred.[32] Thus, treatment of preoperative anemia might be particularly important in these patients.

Intraoperative Period

Surgical techniques have improved in the last decade, and current procedures employing minimally invasive techniques result in decreased blood loss and transfusions synergistic to the goal of Patient Blood Management. This is well established in operations that have changed from an open to a (robotic-assisted) laparoscopic procedure.[33,34] However, far from all operations have changed from an open to a (robotic-assisted) laparoscopic procedure, and within each surgical technique blood loss depends on meticulous hemostasis which is a key aspect of Patient Blood Management.

The use of restrictive erythrocyte transfusion triggers is standard in all Patient Blood Management programs.[11,20] For the majority of patients a transfusion threshold of less than 70 g/l is adequate,[35] and for high-risk cardiac surgical patients, a threshold of less than 75 g/l has been shown to be safe.[36,37] Cell salvage and retransfusion is also an important part of Patient Blood Management programs and in a recent comprehensive meta-analysis has been shown to be associated with a reduction of allogeneic erythrocyte transfusions and a reduction of infection rate, length of hospital stay, and mortality.[38] Acute normovolemic hemodilution is another autotransfusion technique and part of some Patient Blood Management programs as well, and is particularly used in cardiac surgical patients with high hemoglobin levels.[39]

Avoiding intraoperative coagulopathy is also important and its detection and treatment is greatly facilitated by monitoring *via* viscoelastic testing (thromboelastography, thromboelastometry) in combination with laboratory testing and a specific coagulation algorithm.[40–44] Ideally, this algorithm should focus on individualized goal-directed treatment of a specific defect detected with coagulation monitoring.[40–44]

Since fibrinogen is a critical hemostatic protein, in bleeding patients the level should be maintained at greater than or equal to 1.5 g/l.[40,45] Fresh frozen plasma (FFP) is not a good source of fibrinogen as the level varies from 1.0 to 3.0 g/l with mean concentrations of ~2.0 g/l (200 mg/dl)[46]; however, with pathogen inactivation, the mean fibrinogen concentration is below 2.0 g/l.[47] Consequently, FFP administration on its own often does not increase fibrinogen concentration,[48] but does cause hemodilution. This might potentially trigger erythrocyte transfusions without treating the underlying coagulopathy. Another source of fibrinogen is cryoprecipitate.[46] However, this is a multidonor product without any antiviral processing and is not available in many countries due to safety concerns.[46]

The success of individualized goal-directed coagulation algorithms has been shown in cardiac surgery,[49] in major obstetric hemorrhage,[50] and in trauma.[42] Importantly, these studies not only show a relevant reduction in allogeneic blood product administration, but also shorter intensive care unit stay and reduced mortality.[42,49]

Of particular relevance is the early adjunctive use of tranexamic acid in bleeding trauma patients,[51] in patients with isolated traumatic brain injury[52] or postpartum hemorrhage,[53] and in cardiac surgery.[54] When given within the first 3 h of trauma, tranexamic acid is reported to reduce mortality. Tranexamic acid can also be used prophylactically in most types of surgery, and close to 200 meta-analyses describe its effectiveness in reducing blood loss and erythrocyte transfusions, and in improving postoperative hemoglobin concentration without evidence of increased thromboembolic complications.[55] Nevertheless, the use of tranexamic acid should be restricted to surgery associated with significant blood loss.

Postoperative Period

Restrictive transfusion thresholds and individualized goal-directed coagulation algorithms remain important in the postoperative period. For the majority of patients the same transfusion thresholds are adequate, like intraoperative thresholds.[35–37] In patients with acute coronary syndrome, several authors agree that a transfusion trigger of a hemoglobin less than 80 g/l might be justified.[56–58] However, an increased prevalence of acute kidney injury[59] and an increased rate of reinfarction in patients with ST-elevation myocardial infarction[60] has been found in transfused patients. Finally, it needs to be stated that most of these patients were not cardiology and not postoperative patients.

Clinicians must remain vigilant on excessive postoperative bleeding and act quickly to control it. Too often ignored is the consideration that anemia persists and may worsen postoperatively but can be successfully treated with intravenous iron and subcutaneous erythropoietin. Treatment of postoperative iron deficiency anemia (hemoglobin, 70 to 120 g/l; ferritin, less than 100 ng/ml or transferrin saturation less than 20%) with intravenous iron improved hemoglobin recovery in the first 4 weeks and reduced postoperative erythrocyte transfusions, postoperative infections, and hospital length of stay.[61] Intravenous iron also increased hemoglobin recovery after gastrectomy[62] and after postpartum hemorrhage.[63] In addition, intravenous iron also reduced fatigue and postnatal depression.[63,64] A recent meta-analysis found that erythropoietin treatment of critically ill trauma patients is associated with a reduction in mortality by 37% (risk ratio, 0.63 [0.40 to 0.79]; $P < 0.0001$) without adverse thromboembolic side effects despite no reduction in erythrocyte transfusions.[65] However, after trauma, iron metabolism is disturbed with reduced availability of iron for erythropoiesis.[66] Future studies should investigate whether a combination of erythropoietin and intravenous iron therapy may provide greater efficacy.

On average, approximately 300 ml of blood are drawn per week in intensive care unit patients.[67] Inevitably, this contributes to anemia and need for erythrocyte transfusions. Therefore, efforts are needed to restrict the number of diagnostic blood draws, to use small volume collection tubes and employ in-line sampling systems.[68]

In the context of perioperative management of patients with coronary stents and dual platelet inhibition, an important consideration is when to restart the preoperative medication to avoid thrombotic events. For patients receiving oral anticoagulation or dual antiplatelet inhibition preoperatively, their medications should be restarted 1 to 3 days postoperatively depending on the postoperative risk of bleeding without a loading dose of P2Y12 platelet inhibitors (*e.g.,* clopidogrel).[23,31]

Overall Success (Medical, Costs)

Implementing multiple Patient Blood Management measures reduces transfusion of allogeneic blood products and improves the outcome of patients substantially.[10–12] This is elegantly summarized in the recent meta-analysis[11] showing a reduction of erythrocyte transfusions by 39%, hospital length of stay by 0.45 day, major complications by 20%, acute renal failure by 26%, infections by 9%, thromboembolic events by 25%, and mortality by 11% (fig. 1).[69]

Based on Australian data in 605,000 patients from four adult tertiary care hospitals,[10] combined yearly savings of at least 6.8 million dollars was achieved across the four hospitals.[70] Similarly, data in 213,000 patients from a single tertiary care hospital in Switzerland show yearly savings of at least 3.1 million dollars.[71] However, these figures only represent direct blood product acquisition costs and thus underestimate the true costs of blood product administration[7] by at least a factor of three, resulting in yearly cost savings of at least 20 million dollars in the four Australian hospitals and 9 million dollars in the Swiss hospital. This staggering sum still does not include the savings due to fewer complications.[70]

Implementation Strategies

Patient Blood Management is increasingly recognized and implemented as a standard of care[70] and many strategies are consistent with best practices and common sense. For clinicians wanting to implement Patient Blood Management in their institution, a first step is to analyze the current situation in terms of preoperative hemoglobin level, prevalence of anemia, hemoglobin values before erythrocyte transfusions, and perioperative erythrocyte, FFP, and platelet transfusions. This data is key to convince the decision makers that "something needs to be done." In addition, such analyses also allow estimation of potential clinical benefits and cost savings. The second step is the introduction of restrictive transfusion triggers in a joint project of anesthesiologists, surgeons, intensivists, and hematologists. The third step is the introduction of an advanced coagulation monitoring and treatment algorithm—again, a joint effort. The fourth step is the early anemia and iron deficiency detection and treatment. Implementing this module may be quite demanding. Of course, it is reasonable to ask surgeons to schedule operations with significant blood loss (greater than or equal to 500 ml or an erythrocyte transfusion rate greater than or equal to 10%) 2 to 3 weeks before surgery. Even if this request is successful, which is not always the case, all of these patients need to be tracked to assure early treatment by the assigned group of physicians (see also: Preoperative Phase section). In this regard, a custom-made computer program tracking all newly scheduled patients in the electronic operating room scheduling program can be very helpful. This program selects the newly scheduled operations with an expected blood loss of greater than or equal to 500 ml or a perioperative erythrocyte transfusion rate of greater than or equal to 10% and alerts those physicians responsible for anemia and iron deficiency treatment, or sends these patients to a specific dashboard.

The decision where to start a Patient Blood Management program depends on many specific characteristics of the hospital. Generally, orthopedic, colorectal, and cardiac surgery services are the best candidates with which to start, given the high prevalence of preoperative anemia and iron deficiency[3] and significant high blood loss potential.

During introduction and maintenance of Patient Blood Management, data need to be collected continuously to show benefit. The documentation of the success is crucial for the buy-in of additional persons, departments and, finally, the Board of Directors.

Once Patient Blood Management has achieved a certain priority in the institution, the creation of a Patient Blood Management committee is helpful. This committee may by co-chaired by the chairpersons of the Departments of Anesthesiology and Hematology. In addition, the main users of blood products such as the Departments of Cardiac Surgery, Transplant Surgery, Trauma Surgery, and Intensive Care Medicine should be represented. The committee coordinates standard operating procedures, establishes the local list of operations with a perioperative erythrocyte transfusion rate of greater than or equal to 10% or an expected blood loss of greater than or equal to 500 ml and may nominate a patient blood manager. In addition, this committee is to formulate a mission statement for the hospital such as "Elective major surgery is performed in patients with a hemoglobin greater than or equal to 130 g/l (men and women) and in the absence of iron deficiency (ferritin greater than or equal to 100 ng/ml and transferrin saturation greater than or equal to 20%)."

All of the aforementioned developments need to be accompanied by continued education and some form of monitoring with feedback. These are key elements in the implementation and maintenance of a successful Patient Blood Management program. Based on these principles, initial success[72,73] and sustainability was achieved in Perth[74] and Zurich.[71]

Additionally, the group of experts[20] conditionally recommend the introduction of Patient Blood Management. They also suggest further research on the effect of Patient Blood Management programs on adverse events and

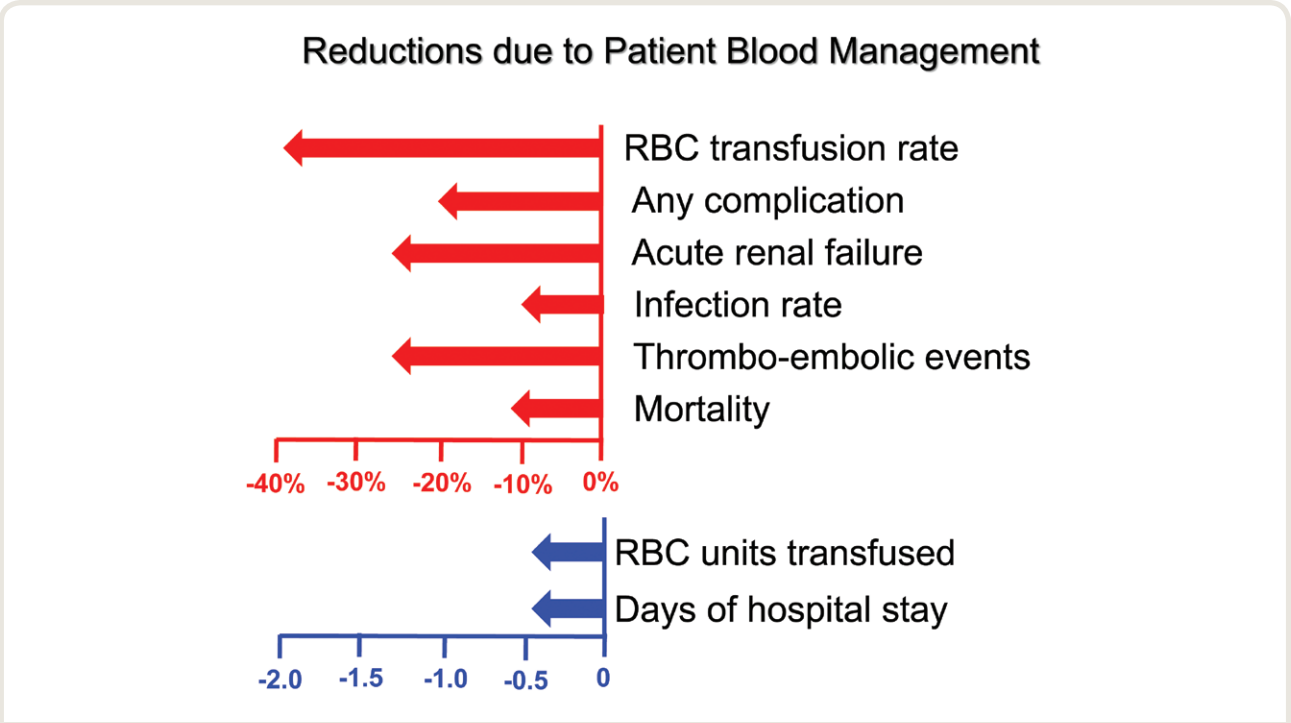

Fig. 1. Implementing Patient Blood Management results in reduced erythrocyte transfusions, major postoperative complications including mortality, and hospital length of stay (according to Althoff *et al.*[11]).

patient-important outcomes, compliance, adherence, and acceptability, as well as cost-effectiveness. While research is always important and will ultimately strengthen the arguments for Patient Blood Management, most of these topics have been favorably answered by the meta-analysis,[11] and by the studies on initial success[72,73] and sustainability from Perth[74] and Zurich[71] (fig. 1).

Limitations and Future Potential

While the primary focus of Patient Blood Management has been on elective surgical patients, urgent or emergent surgical procedures performed can also benefit from many of the strategies (table 1). As has been shown in cardiac surgery,[19] it is never too late to treat preoperative anemia or iron deficiency, a consideration that such treatment should be successful in other surgical disciplines as well. In other patient groups including trauma, anemia, and iron deficiency, treatment with hematinic drugs may be started in the early postoperative phase. In addition, Patient Blood Management measures can also be applied in nonsurgical disciplines as reports suggest, this facilitates a reduction of transfusion of allogeneic blood products and cost savings.[74]

Some centers have not yet started the structured implementation of Patient Blood Management, which should be considered as the new standard of care.[70] Although others have begun easing into Patient Blood Management by changing local transfusion thresholds, greater gains will be achieved by the implementation of other measures such as treatment of perioperative anemia and iron deficiency and advanced coagulation management.

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