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REVIEW ARTICLE

Patient blood management program: individualized approach and strategies for optimization based on three pillars

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Abstract

Implementing the patient blood management (PBM) program is a new concept in our country. It is responsible for optimizing the use of blood components, minimizing their administration, and replacing them with other agents, such as thrombopoietin receptor analogs. However, the main objective is to improve the patient's outcome. The PBM addresses three main pillars, the first includes the comprehensive evaluation of the patient, a situation that involves the anesthesiologist and physicians related to the program. The second pillar is to reduce blood loss through minimally invasive methods, antifibrinolytics, and blood recovery systems. The third is based on the patient's tolerance to anemia, increasing oxemia, and maintaining operative volemia. The relevance of these initiatives in Mexico is to improve the management of blood resources, causing a considerable impact on public health and its sustainability.

Keywords: *Transfusion. Blood Management Program. Blood component. Blood derivative. Hemorrhage.*

Introduction

The concept of a patient blood management (PBM) program was created by the Australian hematologist James Isbister in 2005, whose objective is to optimize the use of blood components, minimizing their administration by replacing them with some other agents, such as erythropoiesis stimulants and, more recently, the use of thrombopoietin receptor analogs[1]. Within the definitions established by the Society for Advanced Blood Management, it is considered that, although reducing transfusion requirements is one of the objectives, the main one is to improve patient outcome[2]. This concept is novel since it focuses attention on the patient, prioritizing hemostatic resuscitation through tools such as viscoelastic tests, patient tolerance to anemia, instituting the autotransfusion policy, and the timely intervention of a multidisciplinary team that includes medical, surgical, and laboratory personnel[1].

The blood management program addresses three main concepts, the first includes the comprehensive evaluation of the patient, a situation that involves the anesthesiologist and physicians familiar with the program, the second pillar is to reduce blood loss through minimally invasive methods, antifibrinolytics and blood recovery systems and the third that is based on the patient's tolerance to anemia, increase oxemia and maintain operative volume[3]. Although the blood management program is based on three fundamental pillars, the second of them is the one that is most frequently

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applied by the surgical teams, made up of the surgeon and the anesthesiologist. In our hospital, being a national reference center, the implementation of the blood management program has demonstrated several challenges, the main ones being the acceptance and use of the different blood derivatives and replacing all the components, followed by the incorporation of a multidisciplinary team for the comprehensive assessment of the patient. At the moment, PBM remains an alternative, with a view to constituting a new health policy to reduce costs and complications around any surgical event.

Although the strategy considers a comprehensive approach based on three pillars, to a greater or lesser extent, each one is applied in routine surgical practice. The ultimate goal of the strategy is to have a coordinated strategy whose objective is not only to save blood components, but also to prevent complications associated with the administration of the different components, reducing hospital stay and morbidity.

First pillar. Anemia: comprehensive patient assessment

Patient assessment is essential to reduce the different risks in both surgical patients and patients under any medical situation. This pillar is implemented by a multidisciplinary group that includes specialist doctors familiar with iron supplementation (internists or hematologists). Anemia is the most common perioperative situation (25-40%). It should be detected and managed before the surgical procedure, and transfusion should be avoided only by the hemoglobin level (e.g., 7 g/dL)[4]. The importance of detecting and correcting anemia is due to the fact that it is significantly associated with an increase in mortality (odds ratio [OR], 2.09; 95% confidence interval [CI], 1.48-2.95) as well as an increase in morbidity[5]. Globally, the World Health Organization considers perioperative anemia when the hemoglobin level is < 13 g/dL in men and 12 g/dL in women, but figures below 11 g/dL are associated with higher in-hospital mortality and a longer length of stay. On this, the most frequent cause of anemia is iron deficiency; its diagnosis is based on the abnormality in iron dynamics (the binding capacity of iron to transferrin, the percentage of saturation, and ferritin)[6]. This evaluation should be made in those individuals who are expected to lose more than 500cc or with a 10% risk of requiring transfusion support during the operative procedure. Despite this, not all patients have anemia, since there are states of iron depletion that can increase hospital morbidity. Ferritin is the parameter of choice for the diagnosis of iron deficiency (< 15 μg/L in adults and < 12 μg/L in children) and in states of iron depletion, but other circumstances such as chronic anemia may cause a significant increase in ferritin (> 100 μg/L), requiring the use of other parameters of iron dynamics for diagnosis (e.g, the percentage of transferrin saturation < 20%)[7]. After diagnosis, it is important to initiate replacement orally or by parenteral formulations. Ng et al. in their review of six randomized clinical trials identified that, although oral iron administration did not reduce blood component administration, parenteral formulations achieved a more rapid improvement in both hemoglobin and iron reserve[8].

Most studies evaluating perioperative management include intravenous formulations and agree on the benefits of pre-operative administration, both for increasing hemoglobin and reducing transfusion requirements. However, due to the heterogeneity of the studies in terms of type of surgery, estimated losses, and time of administration, it is difficult to establish robust recommendations[9]. Another option includes the combination of parenteral iron in conjunction with erythropoietin, on this Donat Spahn and collaborators in a randomized double-blind trial in patients who would undergo elective cardiac surgery (505 patients with anemia or iron depletion) reported the benefit of the administration of reduced doses of parenteral iron in conjunction with erythropoietin (20 mg/kg ferric carboxymaltolate, 40,000 U of subcutaneous erythropoietin alpha), subcutaneous Vitamin B12, and folates on hemoglobin levels, reticulocytes, and reduction in erythrocyte unit transfusion requirements[10].

This has been replicated in several series where the combination of iron, erythropoietin, or other hematins is useful for the management of perioperative anemia. In this regard, in cardiovascular surgery, Weltert et al. reported the benefit of erythropoietin administration (80,000 units of recombinant erythropoietin) 2 days before surgery, identifying that individuals with a figure < 13 g/dL are the ones who benefited the most, significantly reducing transfusion needs ($p < 0.0005$)[11]. The combination of carboxymaltose iron with erythropoietin has been tested in other types of surgeries. Bernabeu et al.[12] analyzed its benefit in patients undergoing hip surgery, demonstrating a benefit on hemoglobin recovery in the post-operative period (10.2 g/L vs. 9.7 g/L) as well as at 60 days, but without an impact on transfusion needs compared to the placebo group. This finding has also been replicated in other series where, despite the fact that the administration of iron before

Table 1. Useful strategies for the evaluation and management of perioperative anemia

Pillars	Intravenous iron	Drug	Presentation	Iron elemental	Infusion time (min)	Dose
First		Iron sucrose	100 mg/5 mL	100 mg	15 a 30	200 a 500 mg/day
		Ferric oxide saccharate	100 mg/5 mL	100 mg	30	100-200 mg
		Hierro dextran	100 mg/2 mL	50 mg/L	60	100-200 mg c/72 h
		Ferric carboxymaltose	500 mg/10 mL	50 mg/mL	15	500-1000 mg/day
	Erythropoietin	**Drug**	**Presentation**	**Route of administration**	**Half-life (hours)**	**Dose**
		Erythropoietin alfa	2000 UI/0.3 mL	SC, IV, IP	19	50-150 UI/kg 1-3 dose/week
		Erythropoietin beta	5000 UI/0.3 mL	SC, IV, IP	20	20-80 IU/kg 1-3 dose/week
		Darbepoetin alfa	300 µg/0.6 mL 500 µg/mL	SC, IV	73	0.45 µg/kg/weekly or c/2 weeks
Second	**Drug**	**Presentation**	**Route of administration**	**Latency (min)**	**Dose**	
	Prothrombin complex concentrate (FII, FVII, FIX, FX, Protein C and S)	500 UI/vial 1000 UI/vial	IV	5	25 IU/kg, maximum 5000 IU, at 8 mL/h	
	Tranexamic acid (Lysine analog)	650 mg 100 mg/mL	VO IV	10	1300 mg c/8 h 1g IV, infusion every 8 h	
	Human fibrinogen	1.5 g/100 mL	IV	60-90	2-4 g 25-50 mg/kg	
	Desmopressin	15 ug/mL Spray 10 µg/dose	IV	30	0.3 µg/kg maximum 20 µg 0.3 µg 2 h before the procedure	
	Cryoprecipitates (FVII, Fibrinogen, FXIII, Vwf)	Unit 5-15 mL	IV	4-12 h	1 unit/5 kg or 10 units	
	Fresh frozen plasma (Fibrinogen, albumin, protein C and S, antithrombin, tissue factor)	Unit 200-250 mL	IV	2-6 h	15-20 mL/kg each/6 h	

SC: subcutaneous; IV: intravenous; PI: intraperitoneal.

surgery improves hemoglobin levels in the post-operative period, it has not been possible to reduce the need for transfusion[13], emphasizing that this requires minimization of blood loss and improvement of hemostatic resuscitation.

The administration of parenteral iron remains an inexpensive and accessible option in most Latin American countries. However, the main challenge lies in implementing effective strategies for its administration, which includes establishing adequate infusion areas and having trained personnel to monitor and manage potential adverse events. Table 1 presents some of the useful strategies for the evaluation and management of perioperative anemia.

Second pillar. Optimizing hemostasis, minimizing blood loss

Optimizing hemostasis is one of the key strategies for reducing blood loss during a surgical procedure. This measure, considered the second pillar of the blood management program, is implemented more frequently than is commonly recognized, both by the surgical team and by the anesthesiologist in its intraoperative

management. In Mexico, hemostatic resuscitation is performed primarily through the use of blood components. The most significant challenge lies in knowing and effectively applying the various types of blood products available (industrialized products) to optimize hemostasis and reduce blood loss.

Normally, the most frequently used blood components are fresh frozen plasma and cryoprecipitates, but there are currently different industrialized derivatives that can replace these blood components. Among the main ones is the concentration of activated prothrombin complex, fibrinogen, Von Willebrand factor, and tranexamic acid as antifibrinolytic therapy. The first is prothrombin complex concentrates (PCCs), which contain coagulation factors (II, IX, X or II, VII, IX, and X) whose hemostatic power is 25 times more potent than fresh frozen plasma, while it can contain heparin, protein C, and protein S[14]. van den Brink et al. in a meta-analysis identified that, although the use of prothrombin complex concentrates (PCC) reduces the need for the use of blood components, its administration does not impact mortality except for patients with trauma (OR = 0.64; CI, 0.46-0.88; p = 0.007)[15]. PCC was originally developed for the treatment of hemophilia B, but with different purified compounds of factor IX, the indications were reduced to the reversal of anticoagulation or congenital deficiency of other less frequent factors[16].

On this aspect, CCP has been analyzed as an option to replace the use of fresh frozen plasma, Ortmann et al. compared its use in patients undergoing endarctectomy, in the group in which CCP was used, a lower blood loss was shown (650 mL [325-1075] vs. 277 mL [175-608], p = 0.008), but without impact with the administration of erythrocyte packages[17]. Recently, Li et al. in a meta-analysis evaluating the benefit of the use of CCP in cardiac surgery agree that although there is no direct impact on mortality (relative risk [RR] = 1.18, 95% CI = 0.86-1.60, p = 0.30), electrical complications or hospital stay, a benefit was demonstrated in the length of stay in the intensive care unit and total bleeding (Mean difference = −248.67 mL, 95% CI = −465.36-−31.97, p = 0.02, I^2 = 84%)[18]. Although plasma can provide coagulation factors, the use of CCP shows certain advantages, such as its quick and easy administration, not requiring cross-referencing or the risk of adverse reaction, but still being limited by the lack of management algorithms outside of cardiac surgery or trauma[19]. For Latin America, the use of this derivative is an option, especially in those cases where rapid resolution of bleeding is required.

The second derivative is fibrinogen, which, similar to PCC, the blood component that provides the highest amount of fibrinogen is cryoprecipitates. This component is very useful in situations where fibrinogen is low or dysfunctional. Fibrinogen is a plasma glycoprotein that is synthesized at the hepatic level. It is the main substrate for the formation of fibrin, and its deficiency can be both congenital and acquired. Similar to other derivatives, the greatest evidence derives from trauma protocols; its benefit can be extended to other types of surgical scenarios[20]. In trauma, the dose is highly variable (2-9 g), as in cardiac surgery (25-50 mg/kg) and even in liver transplantation (50 mg/kg), emphasizing that its consumption is almost immediate for the formation of a clot, and the efficacy of this intervention must be carried out through different viscoelastic tests[21]. In the absence of fibrinogen supplements, the blood component that contains the highest amount is cryoprecipitates (10-20 g/L), but other components, such as fresh plasma (400 mg in 200-250 mL) or platelets (300 mg in 200-250 mL), contain minimal amounts[22]. Due to its dynamism and interaction with coagulation activation complexes, the strategy based on thromboelastography (TEG) is superior to a support based on hemostasis tests (prothrombin time, international normalized ratio, and partial thromboplastin time) in various situations, such as trauma or cardiac surgery, and there are even methods for calculating fibrinogen based on the amplitude of the rotational thromboelastometry (ROTEM)/FIBTEM (Fibrinogen thromboelastometry test) maximum clot firmness (MCF in FIBTEM) that are useful for optimizing fibrinogen supplementation[23].

Monitoring through viscoelastic testing

TEG and ROTEM are similar techniques used to assess hemostasis and blood clotting in real time. Both techniques measure the elasticity and stability of the clot formed in a whole blood sample (340 μL), but differ in their principle of operation[24]. TEG uses a piston or needle in the center of a cup that measures the resistance of the clot as the cup is gently rotated, generating a graph showing parameters such as reaction time (R), clot formation time (CFT) (K), α angle, maximum amplitude, and clot lysis at 30 min (LY30). On the other hand, the ROTEM rotates the cup instead of the piston and measures the resistance of the clot generated, providing equivalent parameters such as coagulation time, CFT, α angle, MCF, and clot LY30. ROTEM offers specific tests such as INTEM, EXTEM, FIBTEM, and APTEM, whereas

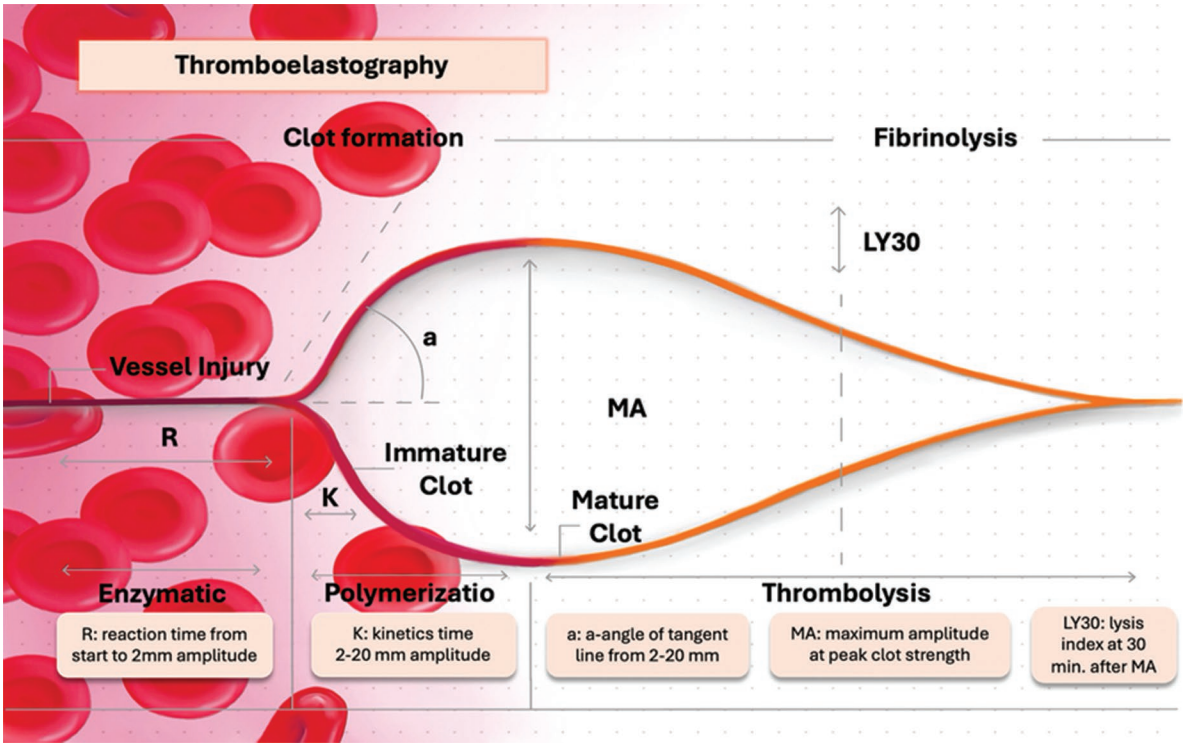

Figure 1. Phases of the thromboelastogram and how it is modified in different perioperative situations.

TEG has variations such as conventional TEG and with coagulation activators[25]. The choice between TEG and ROTEM depends on availability, but both allow for the establishment of guidelines for the transfusion of both components and blood derivatives during surgery, trauma, or situations that alter the stability of a clot, such as liver disease[26]. Various situations can affect the curve generated by the TEG or ROTEM, such as the use of anticoagulants, antiplatelet agents, deficiency of coagulation factors or states of fibrinolysis, giving for example a lengthening of the R time in situations such as severe bleeding or deficiency of coagulation factors, whereas in situations such as hypofibrinogenemia or dysfibrinogenemia the Alpha Angle will be reduced and in very severe states of fibrinolysis the Ly30 will be prolonged. In Mexico, hemostatic evaluation through different viscoelastic tests is becoming more and more common; its use has extended from liver transplantation to resuscitation strategies and, more recently, incorporation into PBM. The implementation of this type of program contributes not only to the saving of blood components but also allows the incorporation of new dynamic hemostatic monitoring strategies, such as viscoelastic tests. Fig. 1 illustrates the phases of the thromboelastogram and how it is modified in different perioperative situations.

Other interventions that optimize hemostatic control

In addition to both correct hemostatic monitoring and the administration of the different components or blood derivatives, there are other drugs that can modify the solidity of the clot, such as antifibrinolytics. Antifibrinolytics are a group of medications that inhibit fibrinolysis, the process by which the body breaks down fibrin clots. Among the best known are tranexamic acid, ε-aminocaproic acid (EACA), and aprotinin. Tranexamic acid works by blocking the binding of plasminogen to fibrin, thus preventing its degradation. It is widely used in surgery and in the treatment of heavy menstrual bleeding[27].

Devereaux et al. in one of the largest studies compared the benefit of tranexamic acid use versus placebo in patients with non-cardiovascular surgery (n = 9535 in total, 4757 treated with tranexamic acid), identifying that bleeding was lower (9.1% vs. 11.7%, RR, 0.76; 95% [CI], 0.67-0.87) in patients treated with tranexamic acid[28]. In civil trauma, the Clinical Randomization of an

Antifibrinolytic in Significant Hemorrhage (CRASH-2) study evaluated 20211 patients, identifying a significant reduction in in-hospital mortality who were administered tranexamic acid (1 g initial dose in 10 min, followed by 1 g every 8 h) compared to those who were administered a placebo (p = 0.0035). A sub-analysis of the CRASH-2 analysis identified that the time to initiation of antifibrinolytic therapy is critical, because early administration (< 1 h) significantly reduced bleeding-associated mortality compared to placebo[29]. This contrasts with the findings of the PATCH-trauma study in which tranexamic acid was administered before arrival at the hospital (1 g before arrival at the hospital and 8 h later), where there was no evidence of an impact on mortality at both 28 days and 6 months after the event[30]. EACA has a similar mechanism of action to tranexamic acid and is used to control bleeding in various clinical contexts, mainly surgical, with similar efficacy[31].

Another drug considered for perioperative loss reduction is desmopressin (DDAVP). This synthetic analog of vasopressin is widely used in mildly expressed congenital coagulation disorders (e.g., hemophilia A or B, Von Willebrand disease), both prophylactically and therapeutically. Outside this scenario, the administration of desmopressin has been evaluated in different surgical scenarios, showing a minimal effect on both the risk of bleeding, the number of blood units transfused, and blood loss, but increasing the risk of hypotension with clinical repercussions. In some clinical situations, such as a history of antiplatelet drug use, the use of DDAVP (0.4 μg/kg × 1 dose) may be beneficial, especially due to the release of factor VIII and von Willebrand factor through the platelet[32].

On this pillar, we can conclude that the timely identification of a bleeding disorder, the selection of the type of blood component, as well as the administration of various derivatives or adjuvants can improve the hemostatic velocity of the individual, reducing the use of blood units and hospital mortality.

Third pillar

The third pillar is based on the patient's tolerance to anemia; it is possibly the least known since it is implemented by the anesthesiology staff to improve the patient's tolerance to blood loss. This principle is based on the ability to release oxygen to each tissue, a situation that is modified by the individual's tolerance to the reduction of their blood volume. This is achieved by improving the individual's cardiovascular performance (avoiding hypotension), increasing arterial oxygen content through increased FiO_2, and preventing a septic process in the post-operative period[33]. Unlike animal models, humans can survive with hemoglobin levels < 2 g/dL, but from levels of 5 g/dL, changes in perfusion can be observed, so for safety reasons, the minimum hemoglobin level for a procedure was postulated between 7 and 8 g/dL. This pillar requires the participation of a multidisciplinary team that contributes to optimizing ventilation methods and resuscitation strategies. Some situations that require a higher hemoglobin level are neurotrauma, as well as in acute coronary syndromes, where the optimal hemoglobin level ranges from 9 g/dL[34]. Some situations that can contribute to greater blood loss are iatrogenic losses, such as taking multiple unnecessary samples, surgical incidents, or the non-use of blood recovery mechanisms.

The management program is a cost-effective option

The fractionation, processing, and storage (activity-based costing method) of blood is one of the parts that generates a constant cost in any hospital[35]. In Europe, Rigal et al. evaluated the cost of this process by establishing a cost of 339.64 euros per unit of blood transfused[36]. In our country, the cost is variable and depends on the type of institution (average of 1750 MXN for a public hospital and 5235 MXN for a private institution)[37]. Another indirect cost derives from the pre-transfusion process (blood typing, cross-testing). In this regard, our institution analyzed the proportion of units transfused over the number of units requested, with only 9.2% of the units requested transfused[38]. This makes any strategy to prevent the use of blood lower the costs of medical care, especially in procedures that require a high consumption of blood components. Roman et al. evaluated 393 randomized controlled trials, which included a total of 54,917 participants, demonstrating that blood management program (PBM) interventions significantly reduce the need for blood component transfusions (RR = 0.60; 95% CI 0.57-0.63; I^2 = 77%). However, no statistically significant impact was observed on mortality at 30 days or during hospitalization (RR = 0.93; 95% CI 0.81-1.07; I^2 = 0%). Although secondary and sensitivity analyses were consistent across clinical settings, intervention types, and study quality, network meta-analysis did not show additional benefits when combining PBM strategies. In addition, the authors concluded that while these interventions reduce transfusions and bleeding, no substantial clinical or economic benefits were achieved[39]. Finally, although the benefit is clear on the

consumption of blood components, more studies are needed in our region to evaluate the economic impact of these strategies.

Conclusion

We consider that the PBM is a useful strategy to save blood components and reduce the different complications related to transfusion. It focuses on the rationalization and optimization of both the components and the different industrialized derivatives in order to reduce morbidity and operative mortality. Despite this, there are still many challenges to implementing this approach in countries with limited resources or without a blood surveillance system. Finally, it should not be forgotten that these policies can generate significant savings in both the short and long term. The relevance of these initiatives is especially critical in Mexico, where improving blood resource management can have a considerable impact on public health and the sustainability of the health system.

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Conflicts of interest

The authors declare no conflicts of interest.

Ethical considerations

Protection of human subjects and animals. The authors declare that no experiments on humans or animals were performed for this research.

Confidentiality, informed consent, and ethical approval. This study does not involve personal patient data, medical records, or biological samples, and does not require ethical approval. SAGER guidelines do not apply.

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