Patient Blood Management: a revolutionary approach to transfusion medicine

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Abstract

Patient Blood Management (PBM) is a multimodal, multidisciplinary approach adopted to limit the use and the need for allogeneic blood transfusion in all at-risk patients with the aim of improving their clinical outcomes. Although PBM usually refers to surgical patients, its clinical use has gradually evolved over the last few years and it now also refers to medical conditions. This review will critically analyse the current knowledge on the use of PBM programmes in surgical and non-surgical patients.

Keywords: patient blood management, blood transfusion, surgery, medical illness, critical care.

Introduction

The term Patient Blood Management (PBM) was first used in 2005 by Professor James Isbister, an Australian haematologist, who realised that the focus of transfusion medicine should be changed from blood products to the patients[1]. PBM is a multimodal, multidisciplinary patient-centered strategy aimed at minimising the use of blood products and improving patients' outcomes[2-5]. PBM has three main objectives: 1) improving red cell mass, including treatments such as erythropoiesis-stimulating agents and iron and vitamin supplements; 2) minimising blood loss, e.g., by optimising surgical and anaesthetic techniques, treatment with tranexamic acid (TXA) and autologous blood salvage; and 3) harnessing and optimising the tolerance of anaemia by promoting maximum pulmonary and cardiac function and the use of a restrictive transfusion threshold[2]. Since it was first described, a number of medical researchers have tried to combine the individual elements of these three PBM objectives in order to promote optimal patient management in various clinical settings. One of the most important fields of application of PBM is the perioperative setting[6,7]. Indeed, some of the risks and complications historically linked with blood transfusions (e.g., transmission of pathogens) have been largely mitigated through advances in transfusion medicine[8,9]. However, anaemia and transfusion have been associated with increased morbidity and mortality in surgical patients, and the systematic application of a PBM programme in the perioperative period has been consistently found to improve patients' clinical outcomes following surgery[10,11]. More recently, PBM programmes have been extended to include non-surgical indications, and medical researchers have attempted to apply this approach to several medical conditions, including critically ill patients in Intensive Care Units, patients with liver disorders or heart failure, and in obstetrics[12-14].

In this narrative review, we summarise current knowledge of PBM programmes and analyse their application in surgical and non-surgical settings.

Search methods

We analysed the available medical literature and studies published on PBM. The MEDLINE electronic database was consulted without specifying a time period and only articles in the English language were selected. The Medical Subject Heading and key words used were: "Patient Blood Management" AND "PBM" AND "blood transfusion" AND "surgery" AND "medical illness" AND "anaemia" AND "critical care". We also screened the reference lists of the most relevant review articles for additional studies not found in our initial literature search. The keywords were also applied to abstracts from the latest international congresses on transfusion medicine.

Patient Blood Management in surgical settings

In association with the improvement of surgical techniques, a number of transfusion and non-transfusion measures have been implemented over the last decades to minimise perioperative blood loss[4]. Among PBM-related transfusion strategies, the issue of the most appropriate red blood cell (RBC) transfusion policy is particularly critical. A number of randomised controlled trials (RCTs) have been carried out on patients' outcomes by comparing restrictive (transfusing when the haemoglobin concentration is <7-8 g/dL)

and more liberal (transfusing when the haemoglobin concentration is <9-10 g/dL) blood transfusion strategies in a variety of surgical settings. At the same time, various systematic reviews and meta-analyses have performed pooled analyses of the data from these RCTs, and their results have been used by scientific societies to provide recommendations and guidelines on RBC transfusion thresholds[15,16]. We have recently performed a critical literature review[11], highlighting the fact that the great majority of experts are in favour of a restrictive transfusion policy, which appears to be associated with lower quantities of blood transfused and a higher level of patient safety than when a more liberal strategy is used. However, these recommendations apply mostly to haemodynamically stable surgical patients, while there is more uncertainty on the optimal transfusion policy in particular categories of patients such as those with acute coronary syndrome, myocardial infarction, neurological injury, acute neurological disorders, stroke, thrombocytopenia, cancer, haematologic malignancies, and bone marrow failure[17]. We concluded our review recommending that well-designed, adequately powered trials should be conducted to assess the appropriate RBC transfusion thresholds in these subgroups of patients.

As far as the non-transfusion PBM-related therapies are concerned, a prominent role is played by TXA[18], which has been widely used to minimise bleeding and exposure to allogeneic blood transfusion in a variety of surgical procedures, particularly in major orthopaedic surgery[19]. Several large RCTs and meta-analyses have consistently confirmed that the intravenous administration of TXA can effectively and safely reduce perioperative blood loss and transfusion requirements in total hip and knee arthroplasty[18]. We have recently performed a meta-analysis of the literature on the safety of intravenous TXA in major orthopaedic surgery[19]. After a meta-analytic pooling of 73 RCTs involving 4,174 patients and 2,779 controls, we observed a similar incidence of venous thromboembolism (2.1% in patients and 2.0% in controls) documenting the safety of this pharmacological treatment in a PBM setting[19]. Interestingly, a recently published prospective cohort study showed that TXA use after the induction of general anaesthesia in total knee arthroplasty can be a fast, inexpensive, and effective opportunity to reduce perioperative blood loss also in patients on chronic antithrombotic treatment[20].

In addition, a recent systematic review and meta-analysis of five RCTs (457 enrolled patients undergoing total hip arthroplasty) concluded that combined intravenous and topical TXA is more effective than TXA alone in terms of reduction in blood loss, haemoglobin decline, and need for transfusion without increasing the rate of thromboembolic complications[21]. The efficacy and safety of topically administered TXA was further supported by a recent study conducted by Perez-Jimeno *et al.* on 249 patients undergoing total hip arthroplasty[22]. In this single-centre, open-label randomised trial, the authors demonstrated that topical TXA was effective in reducing both post-operative RBC loss and transfusion rates with good tolerance and no thromboembolic complications[22].

Another important target of a PBM-based approach is the pharmacological correction of perioperative anaemia, which has a negative effect on patients' health. It is usually associated with prolonged hospitalisation, an increased rate of post-operative complications (especially infections) and, finally, a lower survival rate[23]. In particular, post-operative anaemia (PA) has a considerable impact on patients' outcomes. PA may be due to various factors, including pre-existing anaemia, perioperative blood loss, frequent blood sampling, and inadequate nutritional intake after surgery[6]. As iron deficiency is a typical feature of the post-operative period, iron supplementation is the main target of a PBM-based approach. In this context, administration of intravenous iron, with or without erythropoiesis-stimulating agents, has been found to be a safe and effective way of correcting anaemia in a variety of major surgical interventions[24-26]. In a recent prospective randomised trial, Khalafallah *et al.*[27] reported that a single post-operative intravenous infusion of ferric carboxymaltose (800-1,000 mg) after major orthopaedic, abdominal or genitourinary surgery, significantly improved haemoglobin and ferritin concentrations. It also reduced the number of transfusions and length of hospitalisation in treated patients compared with controls. Similar results were observed in a retrospective, single-centre study conducted by Laso-Morales *et al.* in 159 patients undergoing colorectal cancer surgery[28]. Compared to standard oral iron therapy, the post-operative intravenous administration of iron sucrose (200 mg up to three times a week) to anaemic patients improved the recovery of haemoglobin levels without adverse events.

In addition, according to an analytical-decision model by Basora *et al.,* as intravenous ferric carboxymaltose is less expensive than other reported PBM modalities in primary knee arthroplasty, pre-operative haemoglobin optimisation with this drug and should be considered in patients with iron deficiency anemia[29].

Combining different strategies increases the benefits of a PBM programme, reducing the rate of allogeneic transfusions after simultaneous bilateral total knee arthroplasty. For example, it was recently shown that the use of intravenous iron supplementation with intra-articular administration of TXA reduces the rate of allogeneic transfusions after simultaneous bilateral total knee arthroplasty[30].

Patient Blood Management in non-surgical settings

A PBM approach has also been tried in a number of medical conditions, with the aim of minimising patients' transfusion requirements and improving their clinical outcomes[31].

An excellent example of a PBM policy applied to a non-surgical setting is provided by advanced liver disorders. Liver cirrhosis is ranked as the 13th most common cause of mortality worldwide. In 2010, it contributed an estimated 1.2% of the 31 million global disability-adjusted life years (DALYs)[32,33]. It is also well known that patients with end-stage liver disease have coagulation abnormalities (primarily thrombocytopenia and enhanced fibrinolysis) that predispose them to an increased bleeding risk (mainly acute upper gastrointestinal bleeding) requiring specific and closer evaluation by physicians[34]. Anaemia is a frequent finding in patients with liver cirrhosis, with a reported prevalence of approximately 60% of cases with a multifactorial etiology; this includes iron/vitamin B12/folate deficiencies, hypersplenism, malnutrition, and complications related to underlying causes such as alcohol-induced marrow aplasia or anaemia related directly to viral liver disease or its treatment[35]. Thus, within the framework of a PBM programme, potentially reversible causes of anaemia should be diagnostically explored and corrected to reduce unnecessary transfusions. This consideration is particularly valid for patients undergoing liver transplantation, as blood transfusion is considered a valid predictor of post-transplant overall survival[36]. Another critical issue of a PBM programme in patients with liver cirrhosis is the appropriate transfusion strategy[35]. Indeed, as previously mentioned, although the majority of national and international scientific societies and health authorities recommend a restrictive transfusion policy[4,37,38], this is not reflected in real-life practice in this category of patients. In a large, retrospective nationwide study conducted in the United Kingdom on transfusion practice for patients with liver cirrhosis, RBCs were transfused in over half of the cases presenting haemoglobin >7 g/dL[39]. In addition, approximately one-third of the patients who were transfused with blood components for prophylaxis received fresh frozen plasma (FFP) whose clinical prophylactic effectiveness in patients with liver disorders was recently questioned by a large meta-analysis[40]. Viscoelastic test-guided management would help to reduce the use of FFP and guide the use of coagulation factor concentrates such as prothrombin complex and fibrinogen concentrate. However, as in non-cardiac surgical settings[41,42], more research is needed in this field[43].

Given the high prevalence of anaemia in critically ill patients, it is not surprising that high transfusion rates, ranging from 33 to 75% according to different studies, have been reported[44]. In this setting, a number of studies have linked the exposure to allogeneic blood transfusions with unfavourable outcomes, such as infections, multi-organ dysfunction, thromboembolic events, heart failure, stroke, acute respiratory distress, and mortality[45]. Meta-analyses of pooled results from several RCTs have consistently shown that restrictive transfusion strategies are effective in reducing transfusion rates with similar or improved clinical outcomes compared with liberal transfusion strategies[46,47]. Besides a restrictive transfusion policy, a PBM programme in the Intensive Care Unit includes other measures (i.e., iron supplementation, optimising coagulation and haemostasis, and reducing blood loss) to ensure the most suitable choice of treatment[44].

The PBM programme has also shown benefits in the field of obstetrics[48,49]. Anaemia is frequent during pregnancy and its treatment is mandatory in order to improve maternal and foetal outcomes[48]. Intravenous iron has been found to be an effective and safe way to correct pregnancy-related anaemia in those patients with intolerance or unresponsiveness to oral iron formulations[50]. High-dose intravenous iron has also proved to be effective in obstetric haemorrhage, in association with other surgical and medical therapies (e.g., TXA, fibrinogen, and viscoelastically-guided supplementation of coagulation factors), in reducing blood loss and the need for blood transfusions[51]. With regards to PBM management during post-partum haemorrhage, Shaylor *et al.*[49] performed a qualitative systematic review of published national and international guidelines. Interestingly, the authors observed significant differences between the various guidelines on the recommendations for transfusion and PBM management in this critical condition, highlighting the need for a standardised PBM approach[49].

Anaemia and iron deficiency are also highly prevalent in patients with congestive heart failure and its correction is mandatory within the framework of a PBM programme[52,53]. Indeed, high-dose intravenous iron therapy has proved to be effective in improving anaemia, cardiac function and, ultimately, patients' quality of life[54].

Conclusions

Patient Blood Management programmes are an extraordinary tool for the improvement of patients' clinical outcomes. Like other treatment approaches, consolidated clinical indications for PBM are subject to continuous evolution and new indications are being identified. Thus, further RCTs are needed to provide the experience required to optimise the PBM approach to both surgical and non-surgical patients. At the same time, national and international health authorities

and medical societies should directly intervene by introducing regulatory measures and actions, issuing recommendations and providing resources to promote the effective implementation of PBM programmes.

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Disclosure of conflicts of interest

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