Patient Blood Management: A Patient-Orientated Approach to Blood Replacement with the Goal of Reducing Anemia, Blood Loss and the Need for Blood Transfusion in Elective Surgery

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Keywords

Patient blood management · Anemia · Transfusion · Blood loss

Summary

Patient Blood Management (PBM) describes an evidence-based, multidisciplinary therapeutic approach. Its focus is on the treatment of the individual patient and as such comprises transfusion therapy and pharmacotherapy. Furthermore, the applicability of PBM is not limited to the perioperative setting but is applicable also to other therapeutic measures and disciplines where significant blood loss is known to occur and where transfusion of blood products is part of the established treatment. PBM is fundamentally based on 3 pillars: (1) optimization of the (preoperative) erythrocyte volume, (2) reduction of diagnostic, therapeutic, or intraoperative blood loss, and (3) increasing individual tolerance towards anemia and accurate blood transfusion triggers. PBM primarily identifies patients at risk of transfusion and provides a management plan aimed at reducing or eliminating the risk of anemia and the need for allogeneic transfusion, thus reducing the inherent risks, inventory pressures, and the escalating costs associated with transfusion.

Schlüsselwörter

«Patient Blood Management» · Anämie · Transfusion · Blutverlust

Zusammenfassung

«Patient Blood Management» (PBM) beschreibt einen evidenzbasierten, multidisziplinären therapeutischen Ansatz. Das Hauptaugenmerk liegt auf der Behandlung des individuellen Patienten und schließt die Transfusions- und Pharmakotherapie mit ein. Darüber hinaus ist die Anwendbarkeit von PBM nicht begrenzt auf das perioperative Setting, sondern ist übertragbar auf andere therapeutische Maßnahmen und Disziplinen, die mit einem signifikanten Blutverlust einhergehen und bei denen die Transfusion von Blutprodukten ein Teil der etablierten Behandlung ist. PBM basiert im Wesentlichen auf drei Säulen: 1) Optimierung des (präoperativen) Erythrozytenvolumens, 2) Reduzierung des diagnostischen, therapeutischen bzw. intraoperativen Blutverlusts und 3) Erhöhung der individuellen Toleranz gegenüber Anämie und restriktive Bluttransfusionstrigger. PBM identifiziert zunächst diejenigen Patienten, bei denen das Risiko einer Transfusion besteht, und stellt einen Behandlungsplan zur Verfügung, der darauf abzielt, das Risiko einer Anämie und den Bedarf für eine allogene Transfusion zu reduzieren oder zu eliminieren und so die mit der Transfusion einhergehenden Risiken, Bestandsengpässe und steigenden Kosten zu verringern.

Introduction

Allogeneic blood transfusion has been propagated as life-saving measure especially by blood donor associations. However, the uncritical use of allogeneic blood transfusions faces increasing criticism based on a number of mostly retrospective analyses of outcome data. These outcome data analyses were able to demonstrate a distinct and direct association between the use of blood products and the frequency of perioperative complications, such as an increased risk of myocardial cardiac infarction, infection, transfusion-associated circulatory overload (TACO), or transfusion-related acute lung injury (TRALI). These events are, in general, linked to a prolonged stay in the intensive care units and/or in the hospital and to an increased mortality [1, 2].

In addition, the supply of allogeneic red blood cell concentrates (RBCs) is limited by nature. It is well known that the number of active blood donors is constantly getting smaller. In addition, the average age of the population is increasing steadily. Bringing these facts together, it can be deduced that Central Europe is likely to face significant shortages in the supply with allogeneic blood products in the near future [3].

Furthermore non-compliance with existing guidelines leads to a significant variability in the use of RBCs, which on the one hand increases the risk for the patients and on the other hand represents a significant burden on the health care costs [4]. Using a full cost analysis, Shander et al. [5] demonstrated that blood transfusion is amongst the most expensive treatments currently in practice, accounting for up to 5% of the total health care costs in developed countries. Therefore, it is evident that measures are required to optimize the use of blood transfusions in order to reduce transfusion-associated complications and costs and to counteract any shortage of supplies.

Patient Blood Management

Patient Blood Management (PBM) describes an evidence-based, multidisciplinary therapeutic approach. Its focus is on the treatment of the individual patient and as such comprises transfusion therapy and pharmacotherapy [6, 7]. Furthermore, the applicability of PBM is not limited to the perioperative setting but is applicable also to other therapeutic measures and disciplines where significant blood loss is known to occur and where transfusion of blood products is part of the established treatment. When evaluating the perioperative period of elective surgical interventions, 98% of all cases of red blood cell transfusions can be predicted when analyzing 3 parameters. These parameters are the preoperative hemoglobin (Hb) level, blood loss, and the transfusion trigger [4]. Based on this finding, PBM is fundamentally based on 3 pillars:

- (1) optimization of the (preoperative) erythrocyte volume,
- (2) reduction of diagnostic, therapeutic, or intraoperative blood loss,
- (3) increasing individual tolerance towards anemia and accurate blood transfusion triggers.

First Pillar: Optimization of the (Preoperative) Red Cell Volume

Prevalence of Preoperative Anemia

Anemia existing prior to elective surgery is in the majority of cases of mild to moderate severity and can be diagnosed in up to 80% of the patients, depending on the underlying disease. Thus, the increased transfusion requirements in anemic patients can only in part be explained by a mild to moderate pre-existing anemic condition. On the other hand, a reduction in erythropoiesis in the postoperative phase leading to anemia is likely to be of major importance in triggering transfusion.

The prevalence of anemia depends on the age of the patient, the underlying disease, and on the planned surgical intervention. It is positively correlated with the age of the patient as it is more often encountered in elderly patients in retirement homes as well as during admission to the hospital. In the western hemisphere, the anemia of approximately one-third of the patients is caused by malnutrition, another third of the patients is thought to be anemic due to inflammatory processes, while the causes for the remaining cases are unknown to date [8]. The frequency of surgical interventions in elderly patients may also have an impact on the incidence of anemia. It is known that the existence of preoperative anemia has a negative effect on the outcome, even if there are no concomitant diseases [9]. Currently, the presence of a preexisting anemia is ignored in most cases and the planned surgery is conducted without any corrective therapeutic measures [4]. This observation is especially noteworthy in the context of the requirement to inform anemic patients preoperatively on their increased risk with regard to anesthesia and surgery and to plan diagnostic and therapeutic measures in parallel. In order to comply with these requirements, patients should be presented to the preoperative outpatient clinic as soon as possible, but at least 3 to 4 weeks prior to the planned surgery. At this occasion, not only the eligibility for anesthesia can be assessed and confirmed but also anemia and other known risk factors can be assessed and – if required – appropriate therapeutic measures can be initiated.

Treatment of the Underlying Disease

As a general rule, any preexisting anemia shall be assessed unless being directly linked to the reason for surgery. Any surgical interventions shall be postponed whenever possible

until the assessment results are available and the outcome of any corrective therapeutic measure can be assessed.

Specific Treatment of Anemia

The most frequent causes for preoperative existing anemia are iron deficiency and anemia of chronic disease, but also a combination of both is observed.

Iron Deficiency-Caused Anemia

For the treatment of iron deficiency anemia, an iron substitution therapy is clearly indicated. The actual extent of iron deficiency in anemic patients can be assessed using the Ganzoni formula [10]. In case the patients do not respond to oral iron substitution, the therapeutic regimen should be changed and iron should be administered intravenously. Several substances are suitable for intravenous iron therapy; however, based on its low incidence of side effects, its higher tolerable maximum dose, and the resulting shorter duration of therapy, ferric carboxymaltose is to be preferred. Iron substitution not only augments the efficacy of a treatment with recombinant erythropoietin but also improves cardiac and renal function and leads to an increased physical performance and a higher quality of life [11].

Anemia Caused by Chronic Disease

Anemia caused by chronic diseases (ACD) is in most cases caused by the chronic activation of the immune system and, in general, is of mild (Hb > 10 g/dl) to moderate (Hb 8.5–10 g/dl) intensity. The incidence of ACD in patients with chronic diseases is up to 95% [12]. The mechanism underlying ACD is the sequestration of iron in the macrophages, an inhibition of the production of erythropoietin and of erythrocyte precursor cells, and a shortened survival time of the erythrocytes, leading to a down-regulation of the iron metabolism [12]. An existing ACD can be used as a marker for an existing underlying disease, but it has also been shown that ACD is linked to a more negative prognosis [13]. Patients with anemia caused by rheumatoid arthritis (RA) have lower levels of erythropoietin compared to patients with anemia due to iron deficiency. In RA patients, the observed anemia is often accompanied by iron deficiency, which commonly indicates a higher degree of severity of the underlying disease. ACD patients in general respond well to erythropoiesis-stimulating agent (ESA) therapy, and therefore ESA treatment in ACD patients with planned surgery should be initiated at least 4–6 weeks prior to the planned surgical intervention. Renal anemia is directly caused by erythropoietin deficiency but is aggravated by iron deficiency, bleedings, or reduced erythrocyte lifespan. Renal anemia is foremost treated by ESA therapy.

ESA in combination with other measures was successfully applied for the reduction of transfusions in various surgical settings [14]. Best results were obtained in patients with a starting Hb level between 11 and 13 g/dl. Quite interestingly, it was observed that, while reducing the transfusion probability, simply increasing the Hb value had a negative impact on the

outcome [15]. This finding is attributed to the fact that the optimal Hb level depends on the underlying disease, and therefore it is difficult to set the individual optimum Hb target level. It has been discussed previously that chronic anemia due to an underlying disease can be regarded as an adaptive mechanism, and the treatment and correction of the anemic symptoms in turn leads to an increased mortality [16]. Under these circumstances, a Hb level of 13 g/dl must not be exceeded, although in some surgical settings even higher preoperative Hb levels would be required in order to prevent transfusions.

Second Pillar: Reduction of Perioperative Blood Loss

Anesthesia and Surgical Technique

Perioperative blood loss is an independent predictor for increased morbidity and mortality, which is further aggravated by the impaired hemostasis caused by blood loss [17]. This risk is not reduced but further aggravated when RBCs are transfused. Therefore, it is imperative to stop bleeding as soon as possible in order to limit the blood loss.

Spinal anesthesia is regarded as being advantageous due to the reduced vasodilation and near-normal intrathoracic pressure [18]. Also, for total intravenous anesthesia, a reduction of blood loss compared to inhalation anesthesia is frequently observed [19], and controlled hypotension is able to keep the operating field free from blood [20]. On the other hand, the combination of anemia and hypotension may cause ischemic optic neuropathy [21]. It is therefore advisable to limit the intensity and the duration of the controlled hypotension to situations where improved surgical conditions in the operating field are required.

Suitable techniques comprise, amongst others, damage control surgery or arterial embolization. Also the choice of the surgical access, forward-looking surgery, and adapting the surgical strategy to conditions emerging intraoperatively in close coordination with the anesthetist allow further control of the intraoperative blood loss. Additionally, modern surgical techniques such as minimal invasive surgery and the use of modern devices such as argon coagulation have led to a significant reduction of blood loss and transfusion [22]. In addition, the introduction of small-size extracorporeal circulatory devices in cardiac surgery led to a massive reduction in the use of transfusions, especially in small children and newborns [23]. The use of fibrin glue or local hemostyptics elevation of the surgical area [24], arterial embolization, use of antifibrinolytics, and short-term hypertensive provocative therapy prior to wound closure in order to identify bleeding sources can further reduce bleeding and subsequently transfusion requirements [25–27]. On the other hand, the results of a meta-analysis in patients undergoing knee replacement surgery showed that the use of tourniquets while reducing the intraoperative blood loss did not lead to a reduction in transfusion requirements [28].

Re-Transfusion of Blood from the Surgical Wound

The amount of wound blood being re-transfused without further processing is limited to 1000 ml in adults, due to the contained unwanted contaminations. In contrast, processed erythrocytes may be re-transfused almost without limitations [29]. Re-transfusion is practically limited only by the fact that blood clotting factors and platelets will be lost in clinically relevant amounts in case of massive blood loss and re-transfusion [30]. Wound blood containing tumor cells can be safely re-transfused after a 50-Gy radiation while bacteria-contaminated wound blood must not be re-transfused at all [31]. In the event of an accidental re-transfusion of bacteria-contaminated wound blood, a therapy with broad-spectrum antibiotics is to be initiated immediately. It is noteworthy that filtration of wound blood using leukocyte-depleting filters reduces but does not eliminate tumor cells or bacteria in the wound blood. Therefore, this technique is not suitable to be routinely used for the processing of wound blood [32].

Optimized Management of Hemostasis and Pharmacological Means to Reduce Blood Loss and Transfusions

In case of significant blood loss of more than 50% of the total blood volume, the consecutively required fluid therapy may cause dilutional coagulopathy and may ultimately lead to multiorgan failure [33, 34]. The negative effects of the transfusion of an allogeneic blood product become apparent only after days or even months.

Stabilizing the hemostatic balance is often difficult because there are no reliable analytical methods. In the clinical routine, it is a demanding task to identify patients with an increased risk for bleedings on the one hand and on the other hand to plan the optimum treatment strategy including type and dosage of the coagulation products in advance [35]. The platelet count may also be misleading, as the number of platelets does not necessarily correlate with the degree of functionality. Point-of-care examinations (e.g. ROTEM®, Pentapharm GmbH, Munich, Germany; TEG, Haemonetics GmbH, Munich, Germany) provide a valuable overview of the viscoelastic properties of the blood, including the fibrinolytic capacity. Using these methods in conjunction with adequate evaluation and planning algorithms led to a reduction in the use of blood products [36].

There are noteworthy differences between emergency and elective surgery in this regard. In acute trauma-induced bleedings, first-line surgical hemostasis accompanied or followed by an aggressive treatment with clotting factors appears to be advantageous. On the other hand, this does not seem to apply to patients undergoing elective surgery with blood loss [37]. In elective surgery patients, there is the option to treat bleeding caused by existing disturbed hemostasis prior to the surgical intervention or immediately when encountered. This com-

prises a comprehensive assessment of the hemostasis, treatment stop with a hemostatically active substance well ahead of the surgery, normothermia, a well-balanced acid-base balance, and a stable circulation. The widely used dual-mode antiplatelet therapy has been shown to be associated with an increased risk of spontaneous or perioperative bleedings [38]. This, however, must be carefully weighed against the then increased thrombotic risk of, e.g., implanted stents [39]. In case of bleedings, coagulation factors should be given as early as possible; however, treatment shall only be initiated after surgical hemostasis was attempted.

The prophylactic use of anti-fibrinolytics in, for example, cardiac and orthopedic surgery led to a reduction of perioperative blood loss and to a reduction in transfusion requirements. Since aprotinin has been withdrawn, tranexamic acid has become the first-line treatment. There are reports on complications after the administration of tranexamic acid, with non-ischemic seizures being the leading adverse effects [40].

Third Pillar: Increasing Individual Tolerance towards Anemia and Accurate Blood Transfusion Triggers

Increase and Use of Individual Tolerance to Anemia

Available experiences with surgical interventions in Jehovah's witnesses repeatedly demonstrated that even extremely low Hb levels can be survived and do not necessarily show higher complication rates, provided that adequate techniques are combined [41]. The aim of the PBM concept is not to allow such extreme circumstances at all and therewith reduce the risk for the patient to the maximum possible extent.

A drop in Hb and, as a consequence, the reduced oxygen transport capacity put a high demand on the cardiovascular system and on the coronary reserve [42]. Therefore, it appears to be only logical to treat cardiac risk factors preoperatively. Secondly, it is of advantage to increase the tolerance to anemia also via improvement of the circulatory condition rather than simply increasing the Hb level alone. Also the pulmonary function should be assessed and oxygen should be administered to improve tissue oxygenation even when a minor reduction of Hb is encountered [43]. Additionally, norepinephrine stabilizes the circulation and leads to a higher anemia tolerance in the short term [44].

Indication for Transfusion of Erythrocytes (Transfusion Triggers)

When applying the concept of PBM, the frequency of ad-hoc transfusions is reduced, and in planned surgery only a small number of surgeries and only a very limited number of patients actually require transfusions at all [45]. The primary goal of the transfusion of RBCs is the increase of the oxygen trans-

port capacity and, consequently, the stabilization or increase of the regional or global availability of oxygen. Nevertheless, there are several other physiological properties of the transfused blood such as volume replacement, increase of viscosity, nitric oxide (NO)-scavenging function and others that need to be taken into consideration as well [46]. In the daily routine, a transfusion is mainly triggered by monitoring the Hb level as the only parameter, and there is broad acceptance that an Hb level between 6 and 10 g/dl should trigger a transfusion [47].

Usage of additional trigger parameters such as hemodynamic parameters or the oxygen extraction rate can reduce transfusion requirements in anemic patients, provided that no organ dysfunction or cardiac ischemia or unstable angina is present [48]. It must be noted, however, that the above-mentioned physiological parameters are nonspecific and often depend on other clinical parameters as well. Global indicators of oxygen supply, such as lactate or base deficits, are easily measured but depend themselves on several therapeutic interventions. Mixed venous and central venous oxygen saturation are used for a goal-directed therapy, but give falsely elevated oxygen extraction rates in septic patients. Even in hypoxic patients, blood pressure and cardiac frequency are often normal and the mental state and urine excretion are unspecific markers for a reduced oxygen supply.

Observational studies in large patient cohorts have shown that the recommended transfusion triggers are not used [4, 49, 50]. This is of special interest since adherence to the recommended restrictive transfusion triggers would be the most efficient and cost-effective means to reduce the number of unnecessary RBC transfusions [51]. It is also common practice to transfuse 2 packs or a multiple of 2 although there is no clinical evidence supporting this behavior. On the contrary, it would be more meaningful to guide transfusions by controlling the Hb level and stop transfusions when the transfusion trigger has been reached. Based on the available knowledge, a decision for transfusion must be based upon a combination of clinical parameters and should be made only in connection with adverse changes in the tissue oxygenation. Finally, any decision to use a transfusion should also take into consideration that the administration of erythrocytes is likely to be disadvantageous for the patient in the medium or long term.

Disclosure Statement

The corresponding author states no conflict of interest with regard to this publication.

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