Preoperative anaemia and patient blood management

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Patient Blood Management (PBM) employs a patient-specific peri-operative multi-disciplinary, multimodal team approach to optimize, conserve and manage patients' own blood [1,2]. PBM aims to identify patients at risk of anaemia and provide a managed plan aimed at reducing or even eliminating the need for allogeneic transfusion with an acceptable risk of anaemia and, as a consequence, at improving postoperative outcome.

Evaluating the peri-operative period of elective surgical interventions, 98% of all cases of red blood cell transfusions can be predicted if 3 parameters are analysed. These parameters are the pre-operative haemoglobin, blood loss and individual transfusion trigger [3]. Therefore, PBM is fundamentally based on 3 pillars (Figure 1) [3]:

1. Optimization of the (pre-operative) red cell count
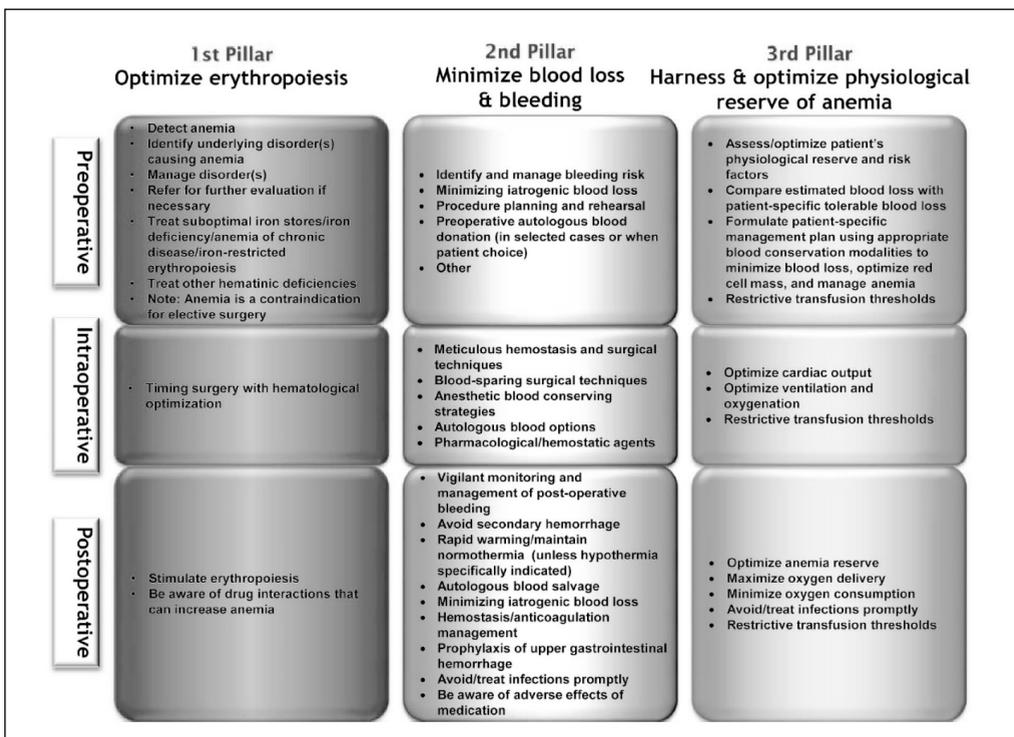
Figure 1: The pillars of patient blood management.
Adapted with permission from Hofmann A, Friedman D, Farmer S, for the Western Australia Department of Health. Western Australian Patient Blood Management Project 2008–2012: Analysis, Strategy, Implementation and Financial Projections. Perth: Western Australia Department of Health, 2007:1–154.

2. Reduction of diagnostic, interventional and peri-operative surgical blood loss
3. Optimizing individual tolerance of anaemia and accurate (restrictive) indication for blood transfusion.

Pre-operative anaemia – Prevalence and risk

In the majority of cases anaemia existing prior to elective surgery is of mild to moderate severity and can be diagnosed depending on the underlying disease in up to 80% of all the patients. However, the threefold increased transfusion requirements of preoperatively anaemic patients can only in part be explained by a mild to moderate pre-existing anaemic condition whereby a reduction of erythropoiesis by the underlying disease is likely to be of major importance in triggering transfusion in the postoperative phase. Besides the underlying disease and the surgical intervention planned, the prevalence of anaemia is positively correlated to 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 approximately one third of the patients anaemia is caused by malnutrition, another third is thought to be caused by inflammatory processes, while the causes for the remaining cases are unknown [4]. The frequency of surgical interventions increased with age which also has an impact on the incidence of anaemia. It is known that the existence of preoperative anaemia is a multiplier of risk factors and has a negative effect on outcome, which may be worse in case of transfusion [5-7]. Currently a pre-existing anaemia is ignored in most cases and the planned surgery is conducted without any corrective therapeutic measures [3]. This observation makes it necessary to inform anaemic patients about their increased peri-operative risk and to plan diagnostic and therapeutic measures. Therefore, 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. Then not only the eligibility for anaesthesia can be assessed and confirmed but also anaemia and other known risk factors can be assessed and, if required, appropriate therapeutic measures can be initiated. Effective anaemia treatment significantly reduces the number of allogeneic transfusions, lowers the risk of anaemia and might improve postoperative outcome [8]. In addition, the enormous costs for transfusion may be reduced [9].

Treatment of anaemia

As a general rule any pre-existing anaemia 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. The importance of assessment and, if possible and meaningful, correction of a pre-existing anaemia increases with its severity.

Anaemia may be the result of iron deficiency alone or in combination with an existing chronic disease. For the treatment of iron deficiency anaemia an iron substitution therapy is clearly indicated, whereby the actual extent of iron deficiency can be assessed by using the Ganzoni formula. If the patients do not respond to oral iron substitution the therapeutic regimen should be changed and iron should be substituted intravenously. Several substances are suitable for intravenous iron therapy based on the low incidence of side effects, higher tolerable maximum dose, and the resulting shorter duration of therapy. Ferric carboxymaltose is to be preferred [10]. In addition, iron substitution not only augments the efficacy of a treatment with recombinant erythropoietin but also improves cardiac and renal function and leads to a higher quality of life [11].

Iron deficiency is frequently observed in patients with chronic infections. In these patients this is regarded as a protective mechanism as iron is a significant contributor to the

proliferation of cancer cells or micro-organisms. Several epidemiologic studies have shown a higher incidence of malignancies in patients with prolonged elevated iron concentration in serum or tissue. In line with this observation a reduction in mortality of 20-30% was observed in patients with diabetes after introduction of a low-iron diet. These findings clearly show that parenteral iron substitution should not lead to abnormally high iron levels. These considerations, however, mainly apply to long-term iron substitution but not to the proposed short-term pre-operative treatment where the risk of iron overload is limited by expected peri-operative blood loss.

Anaemia associated with chronic diseases (ACD) is caused by chronic activation of the immune system and, in general, is of mild (Hb>10g/dL) to moderate (Hb 8.5-10g/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, inhibition of the production of erythopoietin and of erythrocyte precursor cells and a reduced 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. Patients with anaemia caused by rheumatoid arthritis (RA) have lower levels of erythropoietin compared to patients with anaemia due to iron deficiency. In RA patients the observed anaemia is frequently accompanied by iron deficiency which commonly indicates a higher degree of severity of the underlying disease. Common to all forms of ACD is erythropoietin deficiency. ACD patients in general, respond well to ESA therapy. Therefore, ESA treatment in ACD patients with planned surgery should be initiated at least 4-6 weeks prior to the planned surgical intervention.

Renal anaemia is directly caused by erythropoietin deficiency but is aggravated by iron deficiency, bleedings, or reduced erythrocyte lifespan. Renal anaemia is routinely treated by ESA therapy. ESA was successfully applied in combination with other measures for the reduction or prevention of transfusions in various surgical settings [13-15]. Best results were obtained in patients with a baseline haemoglobin level between 11 and 13 g/dL. Quite interestingly it was observed that while reducing the transfusion probability, simple increase of the haemoglobin value had a negative impact on the outcome. This finding is attributed to the fact that the optimal haemoglobin level depends on the underlying disease. Therefore it is difficult to set the individual optimum haemoglobin target level [16]. It has been discussed previously that chronic anaemia due to an underlying disease can be regarded as an adaptive mechanism. As a consequence, treatment and correction of anaemic symptoms may lead to an increased mortality. In intensive care patients the treatment with ESA has been shown to be effective in reaching higher haemoglobin levels. On the other hand, transfusion rate and mortality were reduced only in acute trauma patients but remained unchanged in all other intensive care patients [17]. This observation was recently supported by the results of a meta-analysis in critically ill patients where no advantages of an ESA therapy were found [18]. Also the total correction of anaemia symptoms in chronic renal disease patients lead to an increased mortality [19]. A meta-analysis of 51 clinical trials showed an increased mortality in the patient group treated with ESA. Furthermore this analysis showed that mortality was highest when higher haemoglobin levels were achieved [20]. This observation is further supported by the results of studies in patients suffering from head or neck cancer, breast cancer, or small-cell lung cancer. A possible explanation of this phenomenon can be either the rapid increase or major fluctuations of the haemoglobin levels. An increase in haemoglobin by more than 1g/dL within a period of 2 weeks was shown to be associated with cardiovascular and thrombotic complications.

To date it is unclear whether these observations also apply to the proposed short-term preoperative ESA treatment. Nevertheless, a haemoglobin level of 13 g/dL should not be exceeded even if in some surgical settings higher preoperative haemoglobin levels would be required in order to prevent transfusions.

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