Commentary

Which should be the target for preoperative hemoglobin optimization?

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Preoperative anemia is an independent risk factor for postoperative morbidity and mortality[1]. However, conceptual, logistical and administrative barriers still remain that hinder the widespread implementation of protocols for their management[2]. One of these barriers is the lack of a globally accepted anemia definition for this patient population[1].

In daily clinical practice, the presence of anemia and its severity are defined according to the hemoglobin concentration (Hb) thresholds established by World HealthOrganization (WHO), namely Hb <12 g/dL for non-pregnant women and Hb <13 g/dL for men[3]. According to these WHO criteria, data from 204 countries revealed that there were 1.8 billion prevalent cases of anemia across the world in 2019, with iron deficiency (ID) being its leading etiology (males: 66%, females: 57%)[4]. In addition, iron deficiency anemia (IDA) was one important cause of years lived with disability, with a higher rate among females[5]. Though widely used, the WHO criteria for the definition of anemia may not be reliable for the classification of non-pregnant women undergoing surgical procedures with expected moderate-to-high blood loss[2]. Women tend to have a lower blood volume than men, but have similar blood losses for the same intervention, which translates into greater relative loss of erythrocyte mass and greater red blood cell transfusion (RBCT) requirements[6].

A study of 1,388 women who underwent cardiac surgery revealed that "borderline" Hb concentrations (12.0-12.9 g/dL) was associated with increased RBCT requirements and prolonged hospital stay compared to no anemia (Hb ≥13 g/dL)[7]. In major abdominal surgery, similar differences have been observed between women who had a preoperative Hb between 12 and 12.9 g/dL and those with a preoperative Hb ≥13 g/dL[8]. In a series of women with Hb <13 g/dL, who underwent surgery for hip fracture, perioperative administration of IV iron (400-600 mg) (No. 252) or IV iron (400-600 mg) + EPO (40,000 U) (No. 174) reduced the RBCT rate compared to those who did not receive treatment (No. 118). However, when stratified by Hb at admission, this reduction was only significant for those with Hb between 12 and 12.9 g/dL[9]. Consequently, most recent clinical guidelines and consensus documents recommended that for patients scheduled for a major surgical procedure a preoperative Hb <13 g/dL, irrespective of gender, should be considered as anemia[10-12].

However, two recent large observational studies in orthopedic surgical patients have challenged this new concept[13,14]. The first one was a planned secondary analysis of data collected during a multicenter study of patients undergoing knee or hip arthroplasty in 131 Spanish hospitals during a single 2-month recruitment period (No. 6,099). This analysis revealed that patients presenting with preoperative anemia were more likely to have general complications and moderate to severe complications. In addition,

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multivariate analysis showed that a preoperative Hb ≥14 g/L was associated with a lower incidence of postoperative complications[1].

The second one was secondary analysis on role of preoperative Hb for identifying patients at increased risk of a length of stay >4 days or readmissions due to medical complications in total hip or knee arthroplasty performed within a well-defined fast-track protocol. The effect of preoperative Hb on a machine-learning model was assessed by calculating SHapley Additive exPlanation (SHAP) values for 3,913 patients stratified by gender and procedure type, respectively. There was a steep increase in SHAP value with a preoperative Hb <14.8 g/dL, irrespective of gender age and procedure type. These data point to a Hb threshold <14.8 g/dL for increased risk of impaired recovery, regardless of gender or age, supporting the reevaluation of preoperative Hb thresholds for defining anemia in the elective surgical setting[14].

These two analyses are restricted to patients undergoing major elective orthopedic procedures, thus limiting the generalizability of their results. In addition, patients' demographic and clinical characteristics (co-morbidities) were taken into account, but not the possible influence of hematinic deficiencies, especially iron deficiency, which were not systematically assessed. It must be borne in mind that a person can lose most of his iron reserves before his Hb concentration falls below the cutoff value for defining anemia. Thus, a normal Hb concentration does not necessarily exclude the presence of iron deficiency, which is frequent, has clinical consequences (especially in patients with co-morbidities), and should be considered a disease on its own right[15]. Thus, the proposed preoperative Hb cutoffs might have been overestimated.

In a retrospective review of a multicenter cohort of patients (No. 3,342; 44.5% women) scheduled for frequent elective surgical procedures (orthopedic, colorectal cancer, cardiac, radical prostatectomy, gynecologic, or resection of liver metastases), the prevalence of preoperative anemia, as defined by Hb <13 g/dL, was 36%[18]. Laboratory parameters for the classification of their hematinic status were available in 2,884 patients. Applying consensus definitions, 70% of anemic patients and 40% of non-anemic patients had either absolute or functional iron deficiency, and 40% of all patients had suboptimal iron stores. As expected, the risk of iron deficiency decreases as Hb concentrations increases[16]. Additionally, around 15% presented with folic acid or vitamin B12 deficiency (more frequently among non-anemic patients)[16], though its impact on postoperative outcomes is presently unknown.

These results may be relevant as data from patients undergoing cardiac or major abdominal surgery show that those with non-anemic iron deficiency are at higher risk of poor postoperative outcomes[17,18]. In a prospective observational study, Roëssler *et al.*[17] assessed mortality, serious adverse events (SAEs), allogeneic blood transfusion requirements, and length of hospital stay during a 90-day follow-up period in 730 patients undergoing elective cardiac surgery. Preoperative non-anemic iron deficiency (as defined by ferritin <100 ng/mL) was independently associated with increased mortality, more SAEs, and prolonged hospital stay after cardiac surgery.

In colorectal cancer surgery, Trentino *et al.*[18] compared 441 patients screened in the pre-operative anemia program with 239 patients not screened. In the screened group, 180 (40.8%) received intravenous iron for anemia and suboptimal iron stores. Applying propensity score weighting techniques with multivariable regression models to adjust for differences in baseline characteristics between groups, they found that screening and treating elective patients pre-operatively for anemia and suboptimal iron stores reduced RBCT requirements and total hospitalization costs (a subrogate of postoperative complications) compared with not screening patients, thus demonstrating cost effectiveness.

In Jørgensen's study[14], the relationship between SHAP values and Hb was defined by an inverted sigmoidal curve, with SHAP values being steadily high for Hb concentration <12.5, g/dL, decreasing steeply when Hb concentration increases from 12.5 g/dL to 14 g/dL. SHAP values keep decreasing very slowly until Hb reaches a concentration of 14.8 g/dL, without further decrease thereafter. This may suggest a reduction in the risk of iron deficiency and its consequences with increasing Hb concentrations.

Should this hypothesis be correct, could preoperative treatment of non-anemic iron deficiency improve postoperative outcome? Data from colorectal cancer patients suggest this is the case[18], and a similar conclusion can be drawn from two studies in cardiac surgery[19,20]. In a prospective, double-blind, comparative, placebo-controlled trial (PROTECT trial)[19], 60 non-anemic

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patients (mean Hb 14 g/dL) undergoing cardiac surgery were randomized 1:1 to perioperatively receive either 1,000 mg IV iron isomaltoside 1,000 or placebo. Compared to placebo, IV iron administration resulted in significantly increased the Hb level (12.6 *vs* 11.8 g/dL, respectively; p=0012) and a higher rate of non-anemic patients (38.5 *vs* 8.0%, respectively; p = 0019) 4 weeks after surgery, with a short-term safety profile similar to placebo.

In RCT of patients with preoperative anemia (No. 253) or isolated iron deficiency (No. 252) undergoing elective cardiac surgery, Spahn *et al.*[20] showed that an ultra-short-term combination treatment with IV iron, subcutaneous erythropoietin alpha, vitamin B12, and oral folic acid reduced RBC and total allogeneic blood product transfusions, with respect to the placebo group. Overall, 73 (30%) serious adverse events were reported in the treatment group versus 79 (33%) in the placebo group. More recently, in a post hoc analysis of a large RCT, Weltert *et al.*[20] assessed the effect of a preoperative 30-day course of oral Sucrosomial® iron (60 mg elemental iron/day, Pharmanutra, Pisa, Italy) in cardiac surgery patients with baseline Hb ≥13 g/dL (No. 185). Though iron parameters were not routinely measured, they found that preoperative iron supplementation resulted in a modest Hb increment (+0.6 g/dL), a reduction of RBCT requirements and a shorter postoperative ICU stay, compared with a control group (No. 169) receiving no additional pre-operative treatment. Collectively, these findings underline the high prevalence of iron deficiency among different surgical patient populations and its impact on their postoperative outcomes[16-20], and highlight the importance of non-anemic preoperative iron deficiency screening and treatment in the context of a comprehensive patient blood management program[10-12].

KEY MESSAGES

- Preoperative anemia and iron deficiency are risk factors for postoperative morbidity and mortality.
- Both preoperative anemia and non-anemic hematinic deficiencies, especially iron deficiency, should be screened and treated, as appropriate.
- According to most recent clinical guidelines and consensus documents, an Hb cutoff of 13 g/dL should be used for defining anemia in patients scheduled for a major surgical procedure, irrespective of gender. This Hb cutoff has been recently challenged, but we consider data inconclusive.
- Waiting for new evidence, the treatment target should be the correction of hematinic deficiencies and attaining a Hb of at least 13 g/dL on admission, with its upper level tailored to patient and procedure characteristics (one size does not fit all!).

DISCLOSURE OF CONFLICTS OF INTEREST

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