

QUESTION 14: What preoperative optimization for anemia can be done to increase the hemoglobin concentration?

RECOMMENDATION: Literature suggests that the administration of iron and/or erythropoietin (EPO) increases preoperative hemoglobin concentration and decreases the need for postoperative allogeneic blood transfusion. However, iron may only be effective for patients with pre-existing iron deficiencies and is associated with many side effects. Given the high costs of EPO, its preoperative administration to avoid transfusion alone has not been found to be cost effective. Further research is required to assess the risks and benefits of preoperative allogeneic blood transfusion.

LEVEL OF EVIDENCE: Limited

DELEGATE VOTE: Agree: 92%, Disagree: 3%, Abstain: 5% (Super Majority, Strong Consensus)

RATIONALE

The current literature presents several strategies to increase preoperative hemoglobin including iron supplementation, human recombinant (EPO) injection and preoperative blood transfusion.

Recommended initial management is correction of any deficiencies (such as iron, folate, ferritin, B12, etc.). If patients are noted to be iron deficient, the hemoglobin level can be raised with iron alone, either intravenous (IV) or oral [1]. Oral iron is cheap but takes two to three months to work [2]. Oral iron formulations are also associated with a high gastrointestinal (GI) side effect profile. A 2015 systematic review and meta-analysis examined 43 randomized controlled trials (RCTs) comparing oral iron vs. IV formulations or placebos and found more GI side effects with oral vs. IV formulations (odds ratio (OR): 3.05), and oral vs. placebo (OR: 2.32). This increase in GI side effects in turn reduces compliance with treatment [3]. Intravenous iron is more expensive but may increase hemoglobin levels in two to four weeks depending on the pre-treatment hemoglobin level and the degree of iron deficiency. Side effects are few and generally mild, but rare cases of anaphylaxis are seen as documented by a systematic review which noted 8 cases out of 2,186 infusions [4].

The use of preoperative iron supplementation to raise preoperative hemoglobin for all patients, regardless of iron status, is a more controversial intervention. This is due to conflicting literature, side effects of treatment and ambiguity as to the length of treatment needed to achieve a demonstrable perioperative hemoglobin improvement. Cuenca et al. demonstrated that the use of preoperative iron supplementation, vitamin C and folate for 30 to 45 days before surgery resulted in lower transfusion rate in primary total knee arthroplasty (TKA) patients (5.8 vs. 32%) without existing hematological deficiencies [5]. A further study by Cuenca et al. from 2004 investigated the use of IV iron given on admission and prior to surgery for patients with femoral neck fractures, again without hematological deficiencies, vs. a control group. They concluded that IV iron resulted in a lower transfusion rate postoperatively [6]. However, a study by Lachance et al. refutes this point and showed no difference in the postoperative transfusion rates of total joint arthroplasty (TJA) patients who participated in iron supplementation for three weeks prior to surgery [7]. In addition, iron supplementation was again associated with high levels of side effects including constipation (33%), heartburn (13.8%) and abdominal pain (12.6%) [7]. One limitation of these studies is that none mention improvements of preoperative hemoglobin levels.

The preoperative administration of EPO has universally demonstrated an increase in preoperative hemoglobin and a decreased need for postoperative allogeneic blood transfusion, but with limitations. In a systematic review [8], eight studies (five RCTs and three cohort studies) were included in investigating the effects of preoperative EPO in conjunction with oral or IV iron in patients undergoing major orthopaedic surgery vs. various control groups [8]. After treatment, the mean preoperative hemoglobin was 14.3 ± 0.3 g/dl in the EPO cohort compared to the control (12.4 ± 0.4) [8]. EPO has also been shown in several studies, including randomized controlled trials, to decrease the postoperative rate of allogeneic transfusion [9].

These studies demonstrate a significant decrease in allogeneic transfusion with EPO as compared to routine care [10–12]. Furthermore, in a meta-analysis spanning 26 trials and 3,560 participants, Alsaleh et al. showed that the preoperative use of erythropoiesis stimulating agents reduced allogeneic blood transfusion in patients undergoing hip and knee surgery (rate ratio (RR): 0.48, 95% confidence interval (CI) 0.38 to 0.60, $p < 0.001$) without an increased risk in the development of thromboembolism [13]. Additionally, the largest prohibitive factor for the use of EPO remains cost [14]. Bedair et al. performed a cost-analysis on preoperative use of EPO in TJA patients to avoid transfusion [14]. They demonstrated that the EPO strategy was more costly compared to no EPO (USD 2,632.00 versus USD 2,284.00) and its cost would need to be less than USD 225/dose for this to change. Similarly, in their RCT, So-Osman et al. reported that the cost per avoided blood transfusion in TJA when using EPO preoperatively was 7,300 euros or approximately 9,000 USD, with the authors concluding that this made EPO prohibitively expensive [9].

The combination of iron supplementation, EPO and tranexamic acid (TXA) has also been studied. Zhang et al. investigated the safety and effectiveness of optimized blood management for patients undergoing elective hip and knee arthroplasty by retrospectively comparing the use of TXA with and without the addition of iron supplementation and recombinant human erythropoietin [15]. This study demonstrated that the use of TXA, iron and EPO decreased total blood loss, the need for transfusion and hemoglobin drop without increasing the incidence of venous thromboembolism or mortality [15].

Another method described to increase preoperative hemoglobin is preoperative blood transfusion. A 2010 systematic review assessed four cohort studies, each with 100 patients or more, that compared preoperative autologous transfusion against usual care [8]. The results suggested that preoperative transfusions reduced the need for postoperative transfusions. However, there was no specific mention regarding the improvements in preoperative hemoglobin concentration, nor investigation into other clinical outcomes or adverse events that may be associated with blood transfusions [8].

In conclusion, there is limited evidence to suggest that routine administration of iron and preoperative transfusions increase preoperative hemoglobin and moderate evidence to suggest that EPO increases preoperative hemoglobin. Oral iron is useful in the setting of iron deficiency, but, when used routinely, it is not particularly effective and has a high rate of side effects, particularly gastrointestinal. EPO has routinely been shown to be more effective at increasing preoperative hemoglobin, but has a high monetary cost.

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