# Supplemental digital content

## Part 1: Clinical studies and reviews in specific types of surgery

### Management: preoperative treatment with iron therapy

#### Abdominal surgery

* The literature search identified one review and two studies of preoperative iron (IV) in patients with preoperative anemia.
* The review, published in 2021, reported that preoperative IV iron increased Hb levels but the included studies did not provide consistent evidence of reduced transfusion of allogeneic blood products or other beneficial outcomes.1
* Both studies were RCTs comparing iron with no intervention.
* One study reported that iron therapy reduced blood transfusions, shortened hospital stay, enhanced restoration of iron stores, and increased mean Hb concentration 4 weeks after surgery.2
* The other study (PREVENTT) reported no significant benefit with iron therapy versus placebo regarding blood transfusion rates.3

#### Cardiac surgery

* Systematic review and meta-analysis determining the effects of treating preoperative anemia or iron deficiency with IV iron in adult cardiac surgery patients, published in 2020: “This meta-analysis suggests that [preoperative] IV iron improves postoperative morbidity in adult cardiac surgery patients with preoperative anemia or iron deficiency”.4 This conclusion was based on pooled data from observational studies indicating benefits with IV iron versus no iron in mortality (relative risk 0.39, p<0.001), transfusion utilization (mean difference −1.22 U allogeneic blood product transfused per patient; p<0.001), renal injury (relative risk 0.50; p<0.001) and length of hospital stay (mean difference −4.24 days; p=0.001).
* Systematic review assessing impact of preoperative IV iron on major outcomes following cardiac surgery, published in 2020: “More evidence is needed to support the administration of preoperative IV iron in cardiac surgery patients”.5
  + Results from this review are shown in **Supplementary table 2**.
* Systematic review assessing the impact of anemia and IV iron supplementation on outcomes in cardiac surgery, published in 2015: “On the basis of currently available evidence, the effect of perioperative administration of IV iron to cardiac surgery patients, alone or in combination with erythropoietin, remains unproven”.6
* Systematic review describing strategies to minimize or avoid allogeneic blood transfusions in cardiac surgery, published in 2014: “Treatment of anemia and improving tolerance of anemia have proved to be effective in reducing allogeneic blood transfusions in cardiac surgery”.7
* The literature search identified seven studies assessing preoperative therapy with iron.8-14 Preoperative anemia was a prerequisite for inclusion in two of the studies and it was an exclusion criterion in two studies.
  + Four of the six studies comparing treatment with placebo or no treatment reported that treatment was beneficial (e.g., increased Hb levels, decreased blood transfusions, or decreased postoperative anemia).8, 10, 11, 13 In one of these studies, an increase in the percentage of patients avoiding blood transfusion was shown to be dependent on IV iron successfully increasing Hb to >13 g/dL before surgery (i.e., the transfusion avoidance rate was not significantly increased versus untreated anemic patients in those receiving IVs iron without achieving Hb >13 g/dL preoperatively).8
  + Of the studies with negative results, one was an assessment of IV iron administered shortly (24 hours) before surgery in non-anemic patients.9 The second study reported that IV iron increased Hb levels among anemic patients, but this increase was modest (median 0.8 g/dL) and there was no significant difference versus untreated controls in the transfusion rate.14
  + One study compared IV iron with oral iron, and there were no significant differences in Hb increments or transfusion utilization.12

#### Surgery for colorectal cancer

* Systematic review evaluating the efficacy of preoperative iron supplementation in the treatment of anemia in surgery for colorectal carcinoma, published in 2015: “In anemic patients who require surgery for colorectal carcinoma, current evidence is of inadequate quality to draw a definitive conclusion on the efficacy of the various measures to treat preoperative anemia.”15
* The literature search identified eight studies assessing preoperative iron therapy, of which five were performed in patients with preoperative anemia and two in patients either with or without preoperative anemia.16-23
  + Two out of three studies comparing treatment with placebo or no treatment reported that treatment was beneficial (e.g., increased Hb levels, decreased blood transfusions).20, 21 The study with negative results was an assessment of IV iron administered 14 days before surgery in patients either with or without anemia.16
  + Three studies compared IV iron with oral iron. In the first, there was no significant difference in the use of blood transfusion, but significantly higher Hb levels were observed in the IV iron group.18 The second study reported that IV iron is more efficacious at improving quality of life scores than oral iron.17 The third of these comparisons reported no significant difference between IV and oral iron in 5-year survival, but preoperative resolution of anemia was associated with significantly improved 5-year survival.23
  + A retrospective study compared IV iron with standard care (oral iron or no iron supplementation) in patients with preoperative anemia.22 Individuals receiving IV iron had lower Hb levels at first presentation than those receiving standard care, but Hb levels on the day of surgery and at postoperative day 30 did not differ between the two groups. There were no significant between-group differences in RBC transfusion, but a lower infection rate was reported in the IV iron group.

#### Orthopedic surgery

* Systematic review of preoperative anemia treatment with IV iron in major orthopedic surgery, published in 2020: “We cannot recommend preoperative IV iron therapy for all patients scheduled for major orthopedic surgery. However, for patients with known iron-deficiency anemia (IDA), we still recommend the preoperative treatment with iron supplementation.”24
* Systematic review and meta-analysis of the clinical effectiveness of preoperative iron in anemic patients undergoing elective total hip (THR) or total knee replacement (TKR), published in 2020: “Preoperative iron in anemic, elective THR or TKR patients, significantly reduces the number of patients and number of units transfused and length of stay. This review lacks high-quality RCTs which might allow us to recommend an optimum treatment modality, but our exploratory analysis suggests IV iron correlates with a greater Hb increase than oral iron.”25
* The literature search identified three studies assessing preoperative iron therapy, of which one was performed in patients with preoperative anemia and two were performed in patients either with or without preoperative anemia.26-28
  + Two of these studies compared treatment versus placebo or no treatment, and both reported that treatment was beneficial (e.g., increased Hb levels, decreased RBC transfusions).26, 27 In one of the studies, treatment comprised IV iron either alone or in combination with erythropoietin.27
  + An uncontrolled study of IV iron in orthopedic patients with IDA reported significantly increased Hb levels, with the maximum increase occurring 2 weeks after treatment.28
* Two studies, one of which was an RCT, compared perioperative IV iron with standard treatment.29, 30 Both studies reported lower transfusion rates among patients receiving iron, with morbidity and mortality rates that were similar to those in the population not receiving IV iron.

### Management: preoperative treatment with ESAs

#### Cardiac surgery

* The literature search identified six studies assessing preoperative therapy with erythropoiesis-stimulating agents (ESAs).13, 31-35 Five of the studies were RCTs and five of them compared ESAs with placebo or no treatment. The studies varied in the ESA treatment regimen (dose, timing of therapy), and use of concomitant iron. Preoperative anemia was a prerequisite for inclusion in four studies and preoperative Hb levels ≤14.5 g/dL were required in one.
  + Five of the six studies reported that ESAs, with or without iron, increased Hb concentrations and/or reduced RBC/blood transfusions.13, 31, 33-35
  + A placebo-controlled study of erythropoietin plus IV iron administered before surgery in transcatheter aortic valve implantation patients with preoperative anemia reported that ESA therapy had no significant effect on RBC transfusion.32
  + One small study compared ESA plus iron with iron alone; ESA plus iron was superior in reducing the percentage of patients receiving RBC transfusion.35
  + None of the studies reported that ESA therapy increased the frequency of thromboembolic events.

#### Orthopedic surgery

* Meta-analysis of RCTs of ESAs in knee or hip arthroplasty, published in 2013: “compared with control, preoperative ESAs reduced ABT (RR: 0.48, 95% CI 0.38 to 0.60, p<0.00001) and increased Hb (mean difference between ESA and control groups: 0.716 g/dL, 95% CI 4.73 to 9.59, p=0.00001).”36
* The literature search identified three studies assessing preoperative therapy with ESA, of which two were performed in patients with preoperative anemia and one was performed in patients either with or without preoperative anemia.27, 37, 38
  + Two of these studies compared treatment versus placebo or no treatment, and both reported that treatment was beneficial (e.g., decreased RBC transfusions, improved recovery from postoperative anemia).27, 37 In one of the studies, treatment comprised IV iron either alone or in combination with erythropoietin.27
  + One study compared IV iron with oral iron as follow-up treatment to erythropoietin, and greater increases in Hb and serum ferritin level were seen in the IV group.38

### Management: perioperative transfusion of RBCs

#### Multiple types of surgery

* In the treatment of surgical patients with septic shock and anemia, restrictive and liberal transfusion strategies were compared by Rygård *et al*., with Hb thresholds of 7 g/dL and 9 g/dL, respectively.39 Transfusion rates were lower with the lower Hb threshold, but there were no significant differences in survival between the two strategies.
* A large study assessed whether the relationship between RBC transfusion and mortality differed by lowest observed level of Hb. Among patients whose nadir Hb levels were above 9 g/dL, RBC transfusion was associated with increased mortality. On the other hand, in patients with nadir levels below 9 g/dL, mortality was not significantly affected by RBC transfusion.40 Length of hospital stay was increased among individuals who received RBC transfusions compared with those who did not receive transfusions, regardless of nadir Hb level.
* Outcomes in elderly patients undergoing non-elective surgery unrelated to trauma were assessed in an observational cohort study.41 Receipt of blood transfusion was associated with significantly increased postoperative morbidity and prolonged hospital stay.

#### Orthopedic surgery

* Systematic review and meta-analysis of restrictive versus liberal strategy for RBC transfusion in orthopedic surgery, published in 2018: “In patients undergoing orthopedic surgery, when compared with liberal transfusion, restrictive transfusion increases the risk of cardiovascular events irrespective of pre-existing cardiovascular disease. Importantly, the increased risk was observed in patients undergoing hip fracture surgery but did not reach significance in those undergoing elective arthroplasty.”42
* Cochrane review of RBC transfusion for people undergoing hip fracture surgery, published in 2015: “We found low quality evidence of no difference in mortality, functional recovery or postoperative morbidity between 'liberal' versus 'restrictive' thresholds for RBC transfusion in people undergoing surgery for hip fracture. Although further research may change the estimates of effect, the currently available evidence does not support the use of liberal RBC transfusion thresholds based on a 10 g/dL Hb trigger in preference to more restrictive transfusion thresholds.”43
* Liberal transfusion was compared with restrictive transfusion (Hb thresholds for transfusion of 10 vs. 8 g/dL, respectively) by Carson *et al*. in two studies of hip fracture patients with postoperative Hb levels <10 g/dL.44, 45 In both studies, there were no significant differences between the two transfusion strategies in mortality or other key outcomes. Similarly, a third study comparing restrictive versus liberal transfusion after hip fracture surgery showed no significant between-group differences in mortality, complications, length of hospital stay or regain of mobility.46
* In a study of elderly patients undergoing hip fracture surgery, receipt of a blood transfusion was associated with a lower incidence of delirium.47 However, another study of hip fracture patients found no differences in delirium between liberal versus restrictive transfusion of RBCs.48

#### Cardiac or cardiovascular surgery

* A 2019 meta-analysis comparing restrictive versus liberal transfusion of RBCs in cardiac surgery patients was performed using data from 13 RCTs.49 There were no significant differences in mortality, myocardial infarction, stroke, renal failure or infection rates between the two strategies, leading the authors to conclude that restrictive transfusion does not lead to inferior outcomes compared with liberal transfusion of RBCs.
* Systematic review and meta-analysis of transfusion triggers for guiding RBC transfusion in cardiovascular surgery, published in 2014: “The results of this meta-analysis do not demonstrate a causal relationship underlying the association between blood transfusion and mortality and morbidity. Further randomized controlled trials are necessary to determine the optimal transfusion strategy for patients undergoing cardiovascular surgery.”50
* Two studies retrieved by our literature search compared restrictive versus liberal transfusion of RBCs in cardiac surgery.51, 52 Restrictive transfusion reduced RBC transfusions without increasing the risk of AKI, bleeding, or short-term complications. However, a third study reported increased risk of cardiogenic shock in elderly patients receiving restrictive versus liberal transfusion.53
* Retrospective study of 31,818 patients undergoing CABG: “Operative mortality was 2.1% overall, 0.6% among patients who were not transfused, and 3.3% in the transfused group (odds ratio, 6.19; p<0.0001). The association between blood transfusion and mortality lessened when controlling for preoperative risk of mortality (odds ratio, 2.99) but remained highly significant (p<0.0001). The association between RBC transfusion and mortality after CABG is highly significant and independent of increased preoperative risk status”.54
* In a study of diabetic patients undergoing elective CABG, significant increases in neutrophil gelatinase-associated lipocalin, creatinine, aspartate aminotransferase and advanced oxidative protein products suggested that RBC transfusions may be associated with increased risk of renal injury.55

### Management: postoperative anemia

#### Cardiac surgery

* A placebo-controlled trial of IV iron was performed in cardiac surgery patients with functional IDA on the first postoperative day.56 IV iron significantly increased the Hb level on postoperative day 14, but there were no differences in blood transfusion utilization or postoperative adverse outcomes.
* Madi-Jebara *et al.* compared postoperative IV iron plus recombinant human erythropoietin with IV iron alone or control in cardiac surgery patients with post-pump Hb 7–10 g/dL.57 There was a non-significant trend towards a lower percentage of patients receiving transfusion in the combination therapy group (17% vs 25% with IV iron and 22% in the control group). There were no significant between-group differences in Hb.

#### Orthopedic surgery

* IV iron was compared with oral iron in an RCT conducted in patients with anemia after undergoing total knee arthroplasty.58 IV iron was associated with significantly greater increases in Hb levels, particularly in patients with preoperative iron deficiency or severe postoperative anemia. Total EQ-5D and performance outcomes were comparable between the groups, but better scores for ‘usual activities’ were observed in the IV iron group.
* In another RCT of patients undergoing total knee arthroplasty, the effectiveness of IV iron administered at the end of the arthroplasty procedure for preventing postoperative anemia was investigated.59 The incidence of anemia at 30 days postoperatively was significantly lower with IV iron versus placebo (34% vs. 62%; relative risk 0.55; p=0.008).
* A cost analysis of postoperative IV iron (iron sucrose or ferric carboxymaltose) showed that this intervention was cost-neutral in patients undergoing total knee arthroplasty or total hip arthroplasty.60 IV iron reduced the allogeneic transfusion rate and did not increase the risk of infection.
* Five RCTs published between 1992 and 2010 showed that oral iron is not an effective treatment for anemia occurring after orthopedic surgery.61-65 Oral iron failed to elicit significant acceleration in the recovery of Hb levels versus placebo.

#### Cardiovascular or orthopedic surgery

* In a randomized, placebo-controlled study, performed in 38 patients with anemia after cardiovascular or orthopedic surgery but no preoperative anemia, IV iron was administered alone or in combination with erythropoietin on postoperative days 1–3.66 RBCs were administered after randomization to two patients in each of the iron groups, compared with four patients in the placebo group. A significantly higher reticulocyte count was observed in the combination group compared with the other two groups on postoperative day 7, although there were no significant between-group differences in 1- or 4-week increases in Hb levels.

#### Surgery for colorectal cancer

* In a study of individuals undergoing surgery for colorectal cancer, patients with postoperative anemia received IV iron, while non-anemic patients did not receive IV iron.67 Iron therapy was associated with improved recovery of Hb levels and no increase in postoperative complications.

#### Trauma or critical illness

* The presence of anemia of inflammation in patients with trauma has generated interest in the use of ESAs in this setting.
* In the two largest trials, which were performed in critically ill patients and together enrolled almost 1500 trauma and 650 non-trauma surgery patients, ESAs increased Hb concentrations in both trauma and non-trauma populations.68, 69
  + ESAs were associated with decreased mortality69 and with reduced RBC transfusion rates,68 although both these effects were seen in only one of the two studies.
  + There was an increase in the risk of thrombotic complications with ESA therapy in one of the two studies, but not in patients who also received heparin as anticoagulation therapy.69
* Three recent meta-analyses assessed ESAs in critically ill and/or trauma patients.70-72
  + One of these included eight trials of ESAs in the general critically ill population; ESA treatment had minimal impact on RBC transfusion or Hb concentration, with no difference in either mortality or adverse events.70 However, in the subgroup of trauma patients, individuals receiving ESAs had lower mortality.
  + A second meta-analysis assessed mortality data from 4391 critically ill patients in 16 trials.71 In-hospital mortality was reduced by ESAs in the overall population and in the group of seven studies that exclusively enrolled trauma patients. The rates of serious adverse events and thromboembolic events were similar between the ESA and comparator groups.
  + The third meta-analysis was performed using data from 2607 critically ill trauma patients from nine studies.72 Treatment with ESAs was associated with improved mortality and no increase in the rate of lower limb deep venous thrombosis. Neurologic results showed that ESAs had no effect on the rates of recovery, moderate disability, severe disability good, vegetative state or death.

#### Urologic surgery

* A retrospective study of single-dose IV iron included a cohort of patients receiving this treatment on the first postoperative day for anemia after urologic surgery.73 A significant increase in Hb was observed 7 days after treatment, although there was no control group for comparison.

### Outcome measures: outcomes associated with anemia

#### Cardiac surgery

* In four studies, anemia (or a low preoperative Hb level) was associated with significant increases in transfusion, adverse events (e.g., major bleeding, composite ischemia, AKI), duration of hospital stay and mortality.74-77

#### Colon surgery

* A large database analysis suggested that preoperative anemia is an independent risk factor for complications and a longer hospital stay after colon surgery.78

#### Orthopedic surgery

* Across six different studies, preoperative anemia (or a low preoperative Hb level) was associated with significant increases in transfusion, complications (both infectious and non-infectious), length of hospital stay and likelihood of postoperative readmission to hospital.47, 79-83
* In a large, retrospective study of patients undergoing total knee arthroplasty, no association was found between preoperative anemia and myocardial infarction, cardiac arrest, or death up to 30 days postoperatively. Conversely, anemia was associated with increased likelihood of respiratory and renal morbidities and greater need for transfusions.84

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