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Review

Iron Deficiency Anemia in Colorectal Cancer Patients: Is Preoperative Intravenous Iron Infusion Indicated? A Narrative Review of the Literature

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Abstract. *Iron deficiency anemia is the most common extraintestinal symptom in patients with colorectal cancer (CRC). Inflammation associated with malignancy leads to functional iron deficiency via the hepcidin pathway, whereas chronic blood loss causes absolute iron deficiency and depletion of iron stores. The assessment and treatment of preoperative anemia is of great importance in patients with CRC, since published data have consistently shown that preoperative anemia is associated with increased need for perioperative blood transfusions and more postoperative complications. Recent studies have documented mixed results regarding the preoperative intravenous iron administration in anemic CRC patients in terms of efficacy for anemia correction, cost-effectiveness, need for transfusions and risk for postoperative complications.*

Anemia is diagnosed in 25-75% of cancer patients who undergo elective surgical resections. As for colorectal cancer (CRC) patients, anemia is considered the most common extraintestinal symptom, appearing in 30-75% of patients (1, 2). Preoperative anemia is reported in approximately 50% and 20% of patients with colon and rectal cancer, respectively. In the postoperative period, the incidence of anemia increases to 77% and 66%, respectively, mainly because of the intraoperative blood loss (3). The etiology of anemia in cancer patients is multifactorial. Iron deficiency anemia- absolute, functional, or combined- is the most common type in CRC patients. Absolute iron deficiency is caused by chronic blood loss from the gastrointestinal tract, whereas functional iron deficiency by the inflammation associated with malignancy and/or increased hepcidin secretion (1, 4, 5).

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Absolute Iron Deficiency

Absolute iron deficiency anemia (AID) is the most common type of anemia in CRC patients, representing about 80% of cases (6). Its manifestation includes low tissue and bone marrow iron stores and decreased transferrin saturation values. The gold standard test for AID is an absent stainable bone marrow iron. Chronic blood loss is the main culprit, due to tumor ulceration, leading to iron stores depletion. Malnutrition is a cofounding factor further contributing to CRC cancer-associated anemia because of inadequate iron intake. In AID, hepcidin is suppressed and causes up-regulation of iron absorption and recycling (7).

Functional Iron Deficiency

Hepcidin, a hormone that is produced in the liver, orchestrates iron homeostasis. Hepcidin expression is increased in chronic inflammatory states, which are mainly mediated by IL-6. Hepcidin binds to ferroportin 1 (iron exporting protein) at the

basolateral membrane of enterocytes, hepatocytes, and macrophages, causing internalization and subsequent lysosomal degradation of the latter, reducing ferroportin expression. Consequently, hepcidin inhibits iron absorption in the duodenum and leads to iron sequestration by macrophages and hepatocytes, leading to hypoferremia, which limits erythroid production from the bone marrow. CRC activates the immune system and inflammatory cytokines such as IL -1, -6, -8, and -10, tumor necrosis factor (TNF-a), and interferon-gamma (IFN-γ) are released. These inflammatory mediators up-regulate hepcidin expression but at the same time they decrease erythropoietin (EPO) production and bone marrow responsiveness to EPO and stimulate erythrophagocytosis by bone marrow macrophages. The abovementioned pathophysiologic processes result in decreased iron availability and iron restricted erythropoiesis by the bone marrow, causing what is now known as functional iron deficiency anemia (FID). The gold standard test for differentiating FID from AID is stainable bone marrow iron. If detectable, the iron deficiency is functional, if absent there may be synchronous AID. Total Iron Binding Capacity (TIBC) and transferrin saturation are other useful variables in the diagnosis of FID (3, 7-9).

Preoperative Anemia

Preoperative anemia negatively affects the patient's clinical outcome and is an independent risk factor associated with a higher risk for postoperative complications, longer hospital stay, and increased 30-day morbidity and mortality (10-12). International guidelines have stated that all patients who undergo elective surgery with estimated blood loss >500 ml should be preoperatively (>2 weeks) screened and appropriately treated for anemia (13, 14).

The preoperative diagnosis and treatment of anemia, as well as the prevention of postoperative deterioration, is considered to be the cornerstone of the management of the anemic patient. The World Health Organization has also published relevant recommendations (12).

Allogeneic Blood Transfusion and Transfusion Related-adverse Events

Preoperative anemia is an important risk factor for increased red blood cell transfusions perioperatively, which are independently associated with poor prognosis in CRC surgical candidates. Many studies have documented the transfusion-related adverse effects. A meta-analysis of Acheson *et al*. regarding allogenic blood transfusions (ABTs) on clinical outcomes in CRC surgery found an increased risk for postoperative infections (surgical site, respiratory, *etc*.) and surgical reintervention with an odds ratio of 3.27 [95% confidence interval (CI)=2.05-5.20, $p<0.001$] and 4.08 (95%CI=2.18-7.62, $p<0.001$), respectively. They also found statistically significant increased risk for all-cause mortality (OR=1.72, 95%CI=1.55-1.91, $p<0.001$), cancer-related mortality (OR=1.71, 95%CI=1.43-2.05, $p<0.001$) and recurrence-metastases-death (combined endpoint, OR=1.66, 95%CI=1.41-1.97, $p<0.001$) (11).

Pang *et al*. conducted a systematic review and metanalysis on perioperative transfusions in CRC cancer surgery and confirmed that they are strongly associated with decreased overall survival (HR=0.33, $p<0.0001$) and cancer-specific survival (HR=0.34, $p<0.0001$). Nevertheless, no effect was found on disease-free survival. In the above meta-analysis, the risk for postoperative infectious, cardiac, and pulmonary complications, anastomotic leak, reintervention, as well as deep vein thrombosis, and allergic reactions were significantly increased (15).

The pathophysiologic mechanism behind ABTs and cancer recurrence or metastasis is not well understood but seems to be associated with immunomodulatory effects combined with the inflammatory microenvironment they cause. ABTs seem to negatively affect innate cellular immunity, by restricting NK cell activity, which serves as a protective mechanism against local cancer spread and metastasis. Moreover, the cytokines that are released as an answer to degraded lipid membrane-derived factors, further promote immunosuppression. Furthermore, transfusion may increase the hypoxia-induced release of angiogenic factors such as vascular endothelial growth factor (VEGF), which seems to produce an environment that favors tumor growth (16).

Apart from the immunomodulation that ABT may cause, the shortage of blood donors and the considerable cost of the transfusion have led to the adoption of more restrictive strategies regarding red blood cell transfusions (1, 14, 17).

The adoption of transfusion protocols following strictly specified hemoglobin (Hb) levels and considering a patient's clinical status can affect positively the clinical outcome. The American Association of Blood Banks recommends the adoption of restrictive strategies: no transfusion is suggested in hemodynamically stable patients with Hb >7 g/dl, including critically ill patients, or for Hb>8 g/dl in patients with underlying cardiovascular disease, or about to undergo cardiac or orthopedic surgery. The profound profits associated with this strategy are cost-effectiveness and the reduction in ABT-related adverse effects and postoperative morbidity (18) .

Iron Administration

The administration of iron in cases of TID and FID can be an alternative for the correction of perioperative anemia in CRC patients. Per os, iron administration has limited therapeutic potential due to inefficient absorption, little tolerance, and long duration of treatment needed to achieve hemoglobin correction and iron stores replenishment before surgery. On the contrary,

Table I. *Summary of studies examining iron administration as a means of reducing ABTs and treating preoperative anemia.*

Author, year, country, (reference number)	Study design	No. of patients	Population/ setting	Primary Outcome reported	Secondary outcomes
Calleja, 2016, Spain (1)	Multicenter observational	266	Colon adenocarcinoma anemic patients	IV iron group lower need for ABT (9.9 *vs*. 38.7 %) $p<0.001$	Statistically significant higher percentage of responders by admission and at 30 days post op in the IV iron group
Wilson, 2017 (3)	Cohort retrospective	205	CRC patients with anemia	IV iron group higher increase of Hb level compared to Usual Care ($p<0.001$)	No significant in ABT reduction, or post op complications
Froessler, 2016, Australia (19)	Randomized control trial	72	Abdominal surgery patients with IDA	IV iron group 60% reduction in ABT	Iron group improved Hb by admission, higher Hb levels 4 weeks after discharge, shorter length of stay
Kam, 2020, China (26)	Propensity score matched study	100	CRC patients with anemia	IV iron group higher Hb level on admission ($p<0.001$) and required less RBC transfusions in preop period $p=0.006$	
Oliver Ng, 2019 (29)	Meta-analysis	Six RCTs	Anemic patients undergoing surgery	Iron therapy did not reduce ABTs	IV iron demonstrated better results than oral in hemoglobin and ferritin levels restoration
IVICA trial, 2019 (23)	Randomized Control Trial	116	CRC patients with anemia randomized to receive oral or IV iron	IV iron significantly better correction than oral	Iron therapy no reduction in ABTs IV iron group patients achieved better quality of life scores than the oral iron group
PREVENTT trial, 2020, multicenter (30)	Randomized control trial	487	Patients undergoing elective major abdominal operations randomized to receive or not IV iron	No reduction in number of transfusions, mortality, morbidity, QoL, among patients	Fewer readmission rate in the intravenous iron group due to complications (statistically significant)

IV: Intravenous; ABT: allogenic blood transfusion; Hb: hemoglobin; IDA: iron deficiency anemia; RCT: randomized control trial; CRC: colorectal cancer; QoL: quality of life.

with parenteral iron administration, poor absorption is bypassed and there are fewer gastrointestinal adverse effects. One possible benefit of iron administration is also that it promotes erythropoiesis by the bone marrow and the red blood cells that are produced have a longer lifespan than the donor's, which are removed earlier from circulation (19).

There is a growing body of evidence that preoperative intravenous iron administration can reduce the number of required perioperative transfusions and, as a result, the correlated morbidity (1, 3, 19). Intravenous (IV) iron is superior to oral preparations in terms of erythropoiesis enhancement, less need for blood transfusions, and less transfusion-related adverse effects and complications. It is also the most cost-effective anemia treatment (17). IV administrated iron is a statistically significantly more effective treatment than oral preparations for preoperative anemia and may be a prognostic factor for less severe postoperative anemia, and better physical performance (20).

Besides, newer IV iron preparations like ferric carboxymaltose (FCM) can be safely administered in 15 minutes and high doses (for example 1,000 mg per infusion) (21, 22). These preparations ensure a greater rise in hemoglobin levels with a delayed iron release due to iron encapsulated in a carbohydrate shell and cause less adverse effects than its oral counterparts. They also ensure fewer clinical contacts since a single infusion releases a significantly higher amount of iron compared to oral preparations (2, 7, 9, 23).

Moreover, the cost-effectiveness of screening and treating preoperative anemia with IV iron in CRC patients undergoing

surgery was recently shown; the cost was reduced in terms of less need for ABTs (40%) and shorter hospital stay with fewer complications. (24)

Intravenous iron in FCM. Current literature suggests that IV administration of FCM in a single dose of 1,000 mg at least 2-4 weeks before an elective operation can raise preoperative hemoglobin concentration and reduce the need for ABT perioperatively. As a result, it is a safe and effective way to treat preoperative anemia and reduce the need for blood transfusions and their subsequent risks (1, 4, 19, 25).

In a multicenter observational study from Spain, involving two cohorts of 266 consecutive anemic patients where 111 received FCM and 155 were not treated with IV iron, it was found that a subject from the no-IV iron group had a chance of receiving an RBC transfusion 5.9 times greater than that in the IV iron group (9.9% *vs*. 38.7%, $p<0.001$). The FCM group had significantly higher responder rates concerning hemoglobin levels, both at hospital admission and 30 days after the operation, and shorter hospital stay ($p<0.001$). The lower ratio of complications that were recorded in the FCM group was not significant (1).

A cohort study with 215 patients with severe anemia concluded that IV iron therapy significantly increased hemoglobin levels compared to the usual care group (no iron) with a better result in the absolute iron deficiency subgroup. The authors suggested that the more severe the anemia (higher transferrin, lower ferritin levels), the more effective is the iron therapy (4).

A small RCT from Australia randomized 72 patients before abdominal surgery in receiving IV iron or not. The IV iron group underwent 60% less ABTs perioperatively (31.25% *vs*. 12.5% $p<0.079$) and received fewer units intraoperatively ($p=0.014$), stayed 2.7 days less in hospital ($p=0.026$), and had a higher increase in Hb by the day of admission ($p=0.01$) and a higher hemoglobin level 4 weeks after the operation ($p=0.01$) (19).

A new propensity-score matched study that matched 38 CRC patients with anemia undergoing elective surgery that received intravenous iron with 62 patients who did not receive iron, demonstrated results in favor of IV iron administration; higher median increase in hemoglobin levels preoperatively ($p<0.001$), higher mean hemoglobin level on admission (10.63 g/dl *vs*. 9.46 g/dl, $p<0.001$), and reduction in red blood cell transfusions (8 patients in the IV iron group *vs*. 30 in the non-IV iron, $p=0.006$) (26).

The IV iron infusion in CRC-associated anemia (IVICA) trial included 116 anemic patients with non-metastatic CRC adenocarcinoma and treated them with either oral or IV iron and recorded perioperative and postoperative data. Three major conclusions were recorded: The first was that red blood transfusions were not reduced with preoperative IV iron administration. Secondly, IV iron administration treated preoperative anemia better than the oral counterpart (median Hb rise 1.55 g/dl *vs*. 0.5 g/dl, $p<0.001$) (23). Lastly, the authors concluded that IV iron administration achieved better clinically significant quality of life scores than the oral counterpart from recruitment to surgery and from surgery to outpatient review, with a positive correlation of Hb rise and better scores (27); however, overall survival was not affected (28).

In a recent meta-analysis, Ng *et al*. evaluated six randomized control trials regarding preoperative iron administration (enteral or parenteral) and its outcomes in preoperative anemia correction, need for red blood transfusions, and clinical outcomes. It was concluded that iron therapy did not reduce ABTs. However, IV injected iron showed better results in hemoglobin and ferritin levels restoration than its oral counterpart. The authors suggested that the included RCTs are underpowered due to small sample size and that further research is mandatory (29).

The preoperative intravenous iron to treat anemia in major surgery (PREVENTT) trial, the latest multicenter, double-blind, parallel-group randomized study that included 487 participants undergoing elective major abdominal operations, found no reduction in the number of transfusions, mortality, morbidity, and no improvement in the quality-of-life scores among patients who did or did not receive IV iron before surgery. The only benefit that was statistically significant was that the IV iron group was readmitted fewer times to the hospital due to complications (30). Key studies are represented in Table I.

Conclusion

In conclusion, since the results of the studies so far remain contradictory in terms of the effect of IV iron administration on the need for red blood cell transfusions more randomized control well-designed trials are needed to assess the efficacy of IV iron administration. These studies should include only patients with specific diseases (*i.e*., CRC patients) in order to further individualize anemia treatment according to the underlying disease. Furthermore, the PREVENTT trial demonstrated that the IV iron group patients had a significantly decreased rate of re-admission and a remarkable increase in Hb at 8 weeks and 6 months post-operation. This result could raise concerns about treating anemic patients in a postoperative setting. The latter might show better outcomes, could be more cost-effective, and safer (30, 31).

Conflicts of Interest

All Authors declare that they have no conflicts of interest.

Authors' Contributions

The Authors contributed to this study as follows: study conception and design: L. Chardalias, A. Gklavas, T. Theodosopoulos, I. Papaconstantinou; data collection: L. Chardalias; analysis and

interpretation of results: L. Chardalias, A. Gklavas, M. Politou; draft manuscript preparation: L. Chardalias, A. Gklavas, M. Politou. All Authors reviewed the results and approved the final version of the manuscript.

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