Commentary

Postoperative anemia: is there a role for iron replacement therapy?

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INTRODUCTION

Postoperative anemia (PA) is a common and significant condition after major surgery[1,2]. Allogeneic blood transfusion is the most widely used method to restore hemoglobin (Hb) levels quickly and effectively, with the aim of restoring adequate oxygen delivery to tissues, which is essential for healing and overall bodily function. However, transfusion is an independent factor of adverse outcomes, including increased rates of infections, cardiovascular events, and prolonged hospitalization[3]. Therefore, restrictive transfusion strategies are recommended to minimize these risks, as long as Hb levels are sufficient to maintain adequate oxygen delivery.

In major surgical procedures, the generally recommended transfusion threshold is a Hb below 7-8 g/dL in asymptomatic and non-ischemic cardiac patients[4]. This threshold has been shown not to increase postoperative complications, to reduce hospital stays and healthcare expenses, and to improve long-term survival rate.

In contrast, PA may hinder early rehabilitation and the return to normal daily activities. However, the evidence in this area is still poor and contradictory. Some studies showed that PA does not significantly affect long-term functional recovery or quality of life, while others suggested that higher Hb could result in more active participation in postoperative rehabilitation and greater functional independence[5,6,7]. Thus, treating PA may associate with improved patient recovery, reduced morbidity and mortality, enhanced quality of life, and decreased healthcare costs.

PATHOPHYSIOLOGY OF POSTOPERATIVE ANEMIA[8]

The pathophysiology of PA involves several mechanisms. Surgical procedures often result in significant blood loss. Additionally, the inflammatory response triggered by surgery can lead to alterations in iron homeostasis, characterized by increased hepcidin levels, which inhibit intestinal iron absorption and mobilization from the stores, leading to functional iron deficiency. This inflammatory response can also hamper erythropoiesis, exacerbating anemia. Moreover, patients may also have underlying conditions, such as chronic disease or malnutrition, contributing to preoperative anemia and worsening PA. It is estimated that a third of patients who attend major surgery are preoperatively anemic, with the highest prevalence in patients with cancer, cardiac surgery or femur fracture.

POSTOPERATIVE ANEMIA TREATMENT: EVIDENCE

Among the various treatment options, iron therapy –particularly intravenous iron [IVI]– has emerged as a potentially optimal approach due to its specific advantages in addressing the underlying pathophysiology of PA[8].

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Firstly, by effectively addressing iron deficiency, postoperative IVI therapy may improve erythropoiesis, and the need for transfusions as suggested by some studies. These studies were mostly observational, used historical controls, and generally involved patients with hospital stays of more than one week[9,10].

In recent years, no clinical trials have been published demonstrating that postoperative or perioperative administration of IVI reduces transfusion requirements in elective surgery. Possibly because technical and care improvements in major surgery have significantly shortened hospital stays. In most patients undergoing hip or knee arthroplasty, for example, the average stay does not usually exceed 3-5 days[11]. Similarly, in radical hysterectomies and laparoscopic colorectal cancer surgeries, the average stay is typically 5-7 days[12], and even in heart valve surgeries, the average stay is ≈7 days. In such a short period, it is unlikely that postoperative IVI could achieve a sufficient Hb increase to reduce transfusion needs, although it can improve Hb in the late postoperative period with other advantages. In patients with significant bleeding and longer hospital stays, including in critical care units, postoperative IVI may possibly have an impact on transfusion needs[13].

Anemia can cause symptoms such as fatigue, weakness, and cognitive impairment, which can severely affect a patient's daily functioning and overall quality of life. Anemia improvement alleviates these symptoms, allowing patients to regain their strength and vitality more quickly. Thus, treating PA could enhance patients' quality of life.

So, the question is: *Does treatment of PA with iron improve vigour, functional recovery, and quality of life?*

Administration of oral iron salts has been shown ineffective at improving PA or patients' outcome, whereas two small studies in cardiac and vascular surgery suggested a benefit from oral sucrosomial iron administration, but more research is needed (**Table I**)[14-22].

Our study published in 2014 demonstrated that postoperative IVI after knee replacement was effective increasing postoperative Hb at one month, particularly in patients with significant iron deficiency or anemia, with an impact on quality of life[23]. Likewise, two clinical trials, one in CABG surgery and another in gastrectomy, showed a significant improvement in Hb at 4-12 weeks postoperatively compared to no treatment or oral iron[24,25].

However, a meta-analysis on the efficacy of postoperative iron therapy to improve patient-centred outcomes highlights that IVI has a moderate impact on improving Hb but does not significantly improve outcomes such as quality of life and functioning. Although the authors acknowledge that the review was based on moderately low-quality evidence, they recommend that PA should not be treated with iron in the entire patient population and that further research is needed on postoperative IV iron for certain high-risk populations[26].

The use of erythropoiesis-stimulating agent (ESA), combined with iron supplements for treating PA, has been little explored. In 2023, Chen H et al. evaluated the effectiveness of epoetin (EPO) and IV iron in increasing hemoglobin levels in patients after large joint replacement, demonstrating non-significant improvements in hemoglobin concentrations at first postoperative week[27].

On the contrary, a multicentre French study has shown promising results in evaluating the impact of anemia treatment on outcomes in predominantly surgical patients admitted to the ICU[13]. Anemia is common in ICU patients, often due to iron deficiency (ID), which is challenging to diagnose amid inflammation. Therefore, the study assessed hepcidin, a marker of ID, to guide treatment in critically ill anemic patients. In this single-blind study, patients were randomly assigned to either hepcidin-guided treatment (IVI alone or with erythropoietin based on hepcidin levels) or standard care. The primary endpoint, length of ICU stays, showed no significant difference between the groups. However, the intervention group demonstrated significantly lower 90-day mortality and improved one-year survival, indicating the benefits of hepcidin-guided ID treatment.

On the other hand, our clinical trial that compared the efficacy of iron carboxymaltose (FCM) versus iron sucrose for the treatment of PA in patients undergoing colorectal cancer surgery, demonstrated that ≈500 mg iron sucrose achieved the same effect on Hb than 1,000 mg FCM, at 30 days. Of note, in this study, most patients with preoperative anemia had received IVI preoperatively, suggesting that iron stores may not need to be replenished in the postoperative period as well[12].

Table I - *Some studies evaluating postoperative oral iron after major surgery*

Authors (year)[ref] Study type	Patients	Baseline Hb (g/dL)	PostOP Hb (g/dL) [weeks]	Hb increment (g/dL) difference	Iron formulation Dose (mg elemental iron) Administration schedule	Hospital stay (days)	GI adverse events (%)	Notes
Cardíac								
Crosby *et al.* 1994[14] RCT	FS: 34	9.4	13.5 [8]	4.1	SF (3×65 mg/day, 8 weeks)	?	61.8	
	MVC: 28	9.5	13.4 [8]	3.9 ***−0.03***	MVC (50 mg/day, 8 weeks)	?	14.3	
	Placebo: 26	9.2	13.6 [8]	4.2	Placebo (8 weeks)	?	19.2	
	Control: 33	9.5	13.4[8]	3.9		?	3	
Venturini *et al.* (2022)[15] Observational	SI: 54	10.1	12.0 [4]	1.9 ***−0.5****	SI (120 mg/day, 10 days+30 mg/day, 10 days; No.=54)	?	No	Treatment started at POD10
	FCM: 52	10.1	12.5 [4]	2.4	FCM (1,000 mg IV, one dose; No.=52)	?	No	
Vascular (Abdominal aorta aneurism repair)								
Lucertini *et al.* (2020)[16] RCT	SI: 26	9.3	11.2	1.9 ***+1.5****	SI (30 mg/day, 30 days)	?	No	Treatment started at POD10
	Control: 25	9.3	9.7	0.4	No iron	?	No	
Hip or knee arthroplasty								
Zauber *et al.* (1992)[17] RCT	FS: 37	10.9(F) 11.4 (M)	11.0 [3] 11.4 [3]	0.1 0.0 ***−0.21***	SF (4×105 mg/day)	? ?	6.5 0	
	Placebo: 42	11.1 (F) 11.2 (M)	12.0 [3] 11.7 [3]	0.1 0.5				
Sutton *et al.* (2004)[18] RCT	FS: 35	10.4	12.4 [6]	2.0 ***0.31***	FS (3×65 mg/day)	?	23	
	Placebo: 37	10.5	12.1 [6]	1.6		?	22	
Weatherall *et al.* (2004)[19] RCT	FS: 33	?	13.3 [10]	 ***0.28***	FS (105 mg/day)	?	?	
	Control: 34	?	12.8 [10]		No iron (folate 5 mg/day)	?	?	
Mundy *et al.* (2005)[20] RCT	FS: 50	9.4 (M) 11.0 (F)	12.5 [6] 13.8 [6]	3.1 2.8 ***0.75****	FS (3×65 mg/day)	?	13[(b)]	No Hb difference at 5 days or 3 weeks
	Placebo: 49	9.5 (M) 11.4 (F)	12.0 [6] 13.3 [6]	2.5 1.9	Placebo	?	12	
Hip fracture repair								
Prasad *et al.* (2009)[21] RCT	FS: 32	10.3	12.4 [4]	2.0 ***0.76****	FS (3×65 mg/day)	?	6	
	Control: 34	9.8	11.2 [4]	1.3	No iron	?	0	
Parker *et al.* (2010)[22] RCT	FS: 150	9.9	12.0 [6]	2.1 ***0.29***	SF (2×65 mg/day)	19	17	
	Control: 150	9.8	11.7 [6]	1.9	No iron	21	0	

F: female; FS: ferrous sulphate; GI: gastrointestinal; M: male; MVC: multivitamin complex (Geritol, SKB); FCM: iron carboxymaltose; RCT: randomised control trial, SI: sucrossomial iron; ?: not shown. Difference in Hb increment between groups are denoted in bold italics; * p<0.05

Additionally, some patients may recover from mild to moderate anemia with dietary iron supplementation, as inflammation decreases within a few weeks, assuming iron stores are sufficient.

However, a concerning aspect of the study was the significantly higher percentage of complications observed in patients treated with iron sucrose. Notably, the iron sucrose used was a copy of the original product (Venofer, Melville, NY, USA). In a separate study, Toblli *et al.* highlighted the risks associated with such copies, noting that no specific safety studies had been conducted for them, and approval was based on data from the original molecule. Toblli's research analyzed various iron sucrose copies and found greater molecular instability, a higher proportion of free iron, and significantly higher oxidative stress, compared to the original product[28].

CONCLUSIONS

The management of PA involves a multifaceted approach, including oral or IV iron therapy, ESAs, and blood transfusions, but also no treatment. Each method has its advantages and limitations, and the choice of treatment should be tailored to the patient's specific condition and needs. Further research is needed to optimize PA treatment and improve patient outcomes.

RECOMENDATIONS[29]

Recently some pragmatic clinical guidance for the management of postoperative anemia and iron deficiency has been published with the aim of improving patient recovery.

- Consider iron therapy, preferably intravenous, in cases of mild to moderate PA with iron deficiency or Hb <10 g/dL due to preoperative anemia or significant surgical bleeding, regardless of iron status.
- In patients with severe PA or those who decline transfusion, consider adding an ESA to IV iron treatment, though evidence for its use in this context is limited and should be evaluated on a case-by-case basis.
- For patients with severe symptomatic PA, consider red blood cell transfusion transfusing one unit at a time with reassessment of additional needs.
- Consider administering IV iron after transfusion, using post-transfusion Hb to calculate total iron deficiency. Ensure follow-up after hospital discharge.

KEY MESSAGES

- PA is highly prevalent in major surgical procedures
- PA increases the risk of transfusion and could hinder early rehabilitation and quality of life
- Overall, postoperative IVI treatment was found to be ineffective in reducing allogeneic blood transfusion (ABT).
- The best way to avoid postoperative ABT is to correct preoperative anemia and ID.
- In most patients, postoperative IVI increases Hb and improves/corrects anemia at 4 weeks after surgery.
- In patients with moderate to severe PA and/or ID, IVI significantly increases Hb with an impact on quality of life.
- PA should not be treated with iron in all patients, only in those significantly anemic and/or iron-deficient.
- More research needed on PA treatment, especially for certain high-risk patient populations.

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