

Review

A Paradigm Shift: Perioperative Iron and Erythropoietin Therapy for Patient Blood Management

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Allogeneic blood transfusion is often restricted due to its adverse effects, a lack of blood supply, and religious or cultural constraints. As a result, patient blood management (PBM) has been gaining attention. PBM is an evidence-based, patient-centered bundle of technologies that manages perioperative anemia and reduces bleeding during surgery. PBM improves the postoperative prognoses. Perioperative anemia is the main concern in PBM; therefore, to diagnose and treat it is important. This review focuses on the perioperative use of oral or intravenous iron and erythropoietin (EPO), in relevant fields such as cardiac surgery, orthopedics, and neurosurgery. IV administration of iron has been controversial due to safety concerns, such as increased risk of infection. However, using IV iron appropriately is beneficial in most surgical settings. Although recombinant human EPO may increase thromboembolic risks, this can be mitigated through various methods including limiting the target Hb level, using it in combination with IV iron, or prophylaxis for deep venous thrombosis. EPO is recommended in patients undergoing cardiac or orthopedic surgery. As PBM becomes globally implemented, the blood management methods, including tranexamic acid, hemostatic agents, and cell salvage have become more variable as well. Among them, administration of iron and EPO would be the most common pharmacologic choices based on current practice. However, controversy still exists. Therefore, further studies on iron and EPO are needed to ensure better and safer patient care.

Key words: Anemia; Iron; Erythropoietin; Bloodless medical and surgical procedures; Perioperative care

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Received 11 Oct 2017

Revised 28 Jan 2018

Accepted 12 Feb 2018

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INTRODUCTION

The idea of Patient Blood Management (PBM) has emerged mainly due to problems caused by blood transfusion and perioperative anemia. This concept is based on the 5 elements suggested by Hofmann et al. [1] (2011): gaps between supply and demand for blood, high transfusion costs, risk of contaminated blood products, adverse outcomes of transfusion, and a paucity of evidence to prove transfusions efficacy. Furthermore, there is a serious issue related to perioperative anemia. The significance of managing perioperative

anemia is particularly underestimated, and medical professionals use blood transfusions indiscriminately to rapidly return hemoglobin (Hb) levels to normal [2,3].

PBM is a group of multi-disciplinary protocols under the concept of 3 pillars that are applied to a patient's clinical course (before, during and after the operation): optimizing red blood cells (RBCs) production, reducing bleeding, and harnessing the tolerance of anemia [1,4]. One of the advantages of PBM is cost-effectiveness. The Department of Health in Western Australia started comprehensive PBM; they experienced cost savings of Australian dollar (AUD)

10,725,750 (approximately \$8,500,000 US dollars) in blood products and hospital-related blood transfusions during the 3 years after PBM initiation [5]. The World Health Assembly of the World Health Organization (WHO) shared some guidelines and recommended PBM to its members in the 63rd session in 2010 [5]. PBM includes various techniques such as oral and intravenous iron supplementation, hemostatic agents, erythropoietin (EPO), tranexamic acid (TXA), and cell salvage.

Among the numerous methods in PBM, iron and EPO therapies were chosen in this review because they are more commonly used pharmacologically compared to transfusion [6]. The aim of this review was to use recent data to demonstrate the effectiveness of PBM using iron therapy and EPO management in clinical departments such as cardiac surgery, orthopedics, and neurosurgery.

THE LIMITATIONS OF BLOOD TRANSFUSION

Allogeneic blood transfusion has contributed to advances in medicine and surgery. However, the threshold for blood transfusions is still controversial. A Canadian critical care trial in 1999 showed that a restrictive transfusion policy (transfusion of RBCs if Hb level is less than 7 g/dL) is possibly more effective than a liberal transfusion strategy (transfusion of RBCs if Hb level is lower than 10 g/dL) except for patients with active coronary ischemia [2]. The National Institute for Health and Care Excellence (NICE) guidelines also encourage restrictive transfusion policy; however, for patients with cardiovascular disease, transfusions are needed if the Hb level is lower than 8 g/dL [7].

Despite restrictive transfusion, there are still some limitations to transfusion, such as blood supply, transfusion risks, and patient refusal of treatment.

First, there is a global blood shortage. For example, the Korean Red Cross, undertaking the essential role in blood services in South Korea, reported in 2014 that the blood supply for transfusion did not match the demand of blood in March and October. After that, in the first half of 2016, there was a shortage of blood supply countrywide, and this phenomenon continued through 2017 [8].

Second, there are some dangers to transfusion. Although allogeneic blood transfusion has contributed to the development of medical and surgical advances, several studies have reported that blood transfusion causes medical problems and worsens the patient's outcome and safety. Risks of transfusion include urticaria (1–3%), anaphylaxis (1 in 20,000 to 1 in 50,000 transfusions), transfusion-related acute lung injury (approximately 1 in 5,000 transfusions), delayed hemolytic transfusion reactions (approximately 1 in 6,000

transfusion units), circulatory or iron overload [9], and infectious diseases such as hepatitis B and C, bacterial sepsis, malaria, and human immunodeficiency virus (HIV) infection. The incidence of adverse events is approximately 0.5–3% [10].

Lastly, there might be some people who cannot receive transfusions due to RBC antibodies or religious or cultural beliefs.

PREOPERATIVE ANEMIA

The WHO defines anemia as the Hb level below 13.0 g/dL in men, 12.0 g/dL in non-pregnant women, and 11.0 g/dL in pregnant women [4]. It is a serious health problem affecting 1 in every 3 or 4 people worldwide; hence, it needs to be considered a disease that should be evaluated and treated [11].

Especially surgical patients commonly have preoperative and postoperative anemia. According to 18 large studies, the average preoperative anemia prevalence was approximately 35% in more than 650,000 surgical patients [12]. Preoperative anemia is closely associated with longer hospital stays, higher mortality, greater blood transfusion needs, and increased postoperative complications [4]. One cohort study of 3,500 patients undergoing anterior cervical discectomy and fusion demonstrated that preoperative anemia is significantly associated with an increase in minor or major complications; pulmonary, renal, or central nervous system complications; blood transfusion needs; and length of hospital stay [13]. Mild anemia increases perioperative complication risk by 30–40%, and this risk increases with the increase in the severity of the anemia. Owing to the deleterious effects of preoperative anemia, major and non-urgent surgeries may need to be rescheduled to diagnose and treat anemia and iron deficiency. It is recommended that patients be assessed at least 30 days before any major planned surgery, and the type of anemia might be distinguished using tests such as blood count test, iron tests, and an inflammation marker test including C-reactive protein (CRP) [4,14].

Preoperative anemia has multifactorial causes including iron or other nutritional deficiencies such as folate or protein, inflammatory cytokines' activation, and diagnostic phlebotomies that many vials of blood are drawn. In a study with 715 patients undergoing major orthopedic surgery, 75 people were anemic. Among them, about 30.8% had nutrient deficiencies, and 30.8% had chronic inflammation, as a cause of anemia [12].

Iron, one of the most important types of nutritional deficiencies, is an essential element in cellular function and oxygen transportation in the human body. Stored iron can be reflected as ferritin levels. A peptide hormone hepcidin targets an iron exporter called

ferroportin on the cell surface. This interaction between hepcidin and ferroportin regulates iron homeostasis, and the expression of hepcidin gets influenced by some physiological conditions. In anemia, iron deficiency, active erythropoiesis, and hypoxia, hepcidin synthesis is decreased in normal homeostasis (Fig. 1). Decreased hepcidin levels increase the iron absorption in the intestines. However, if the absorbed amount of iron is less than the lost amount, stored iron would be exhausted. Then, the patient gets iron deficiency, and if this repeats again and again, iron deficiency anemia (IDA) occurs. IDA comprises 3 stages: the first stage is the paucity of stored iron, the second stage is erythropoiesis with iron deficiency, and the third stage is lack of iron supply which cannot return Hb levels to the normal levels [15].

In case of anemia of chronic inflammation, cytokines including interleukin-1 (IL-1), IL-6, IL-10, and tumor necrosis factor (TNF)- α are produced. Subsequently, expression of hepcidin is increased (Fig. 1). This phenomenon is related to a decrease of serum iron level and an increase of serum ferritin levels, thus limiting iron's availability for erythropoiesis. Moreover, there is resistance to EPO, and the responses to EPO are reduced, resulting in chronic inflammation-induced anemia [16].

In conclusion, the prevention and appropriate management of preoperative anemia through PBM can decrease mortality and the need for intensive care in patients undergoing surgeries. One PBM strategy that can be commonly and importantly used at this stage is to offer patients iron and/or EPO management.

IRON THERAPY FOR PBM: ORAL AND INTRAVENOUS IRON SUPPLEMENTATION

According to various studies, oral or IV iron treatment before orthopedic, colorectal, or gynecological surgery contributes to treating anemia and reducing blood transfusion rates and duration of admission days [14,17]. A systemic review of 72 randomized clinical trials (RCTs) including 10,605 subjects demonstrated that IV iron raises Hb levels and lowers the risk of needing a blood transfusion [18].

Iron can be administered either orally or intravenously. When there is enough time to elevate Hb levels to normal levels before surgery (more than 6 weeks), oral iron supplements would usually be chosen for replacing iron reserves. After taking iron orally, Hb levels start to increase 2–2.5 weeks later, and Hb levels return to normal values 2 months later. In contrast, after taking intravenous iron, Hb levels start to increase only after 7 days [19,20]. Most studies conducted focused on preoperative iron therapy, but there are also some recent data using postoperative intravenous iron [21,22]. Khalafallah and colleagues conducted a prospective RCT with 201 patients undergoing major orthopedic, abdominal, gynecological, urological, and other operations. They demonstrated that postoperative administration of intravenous ferric carboxymaltose (FCM) significantly improves Hb recovery at 4 weeks and serum ferritin level at both 4 and 12 weeks [22].

There are several oral iron formulations such as polysaccharide iron complexes, ferrous sulfate, fumarate, and gluconate. A dose of 100–200 mg daily (approximately 70 mg of iron, 3 times a day) is

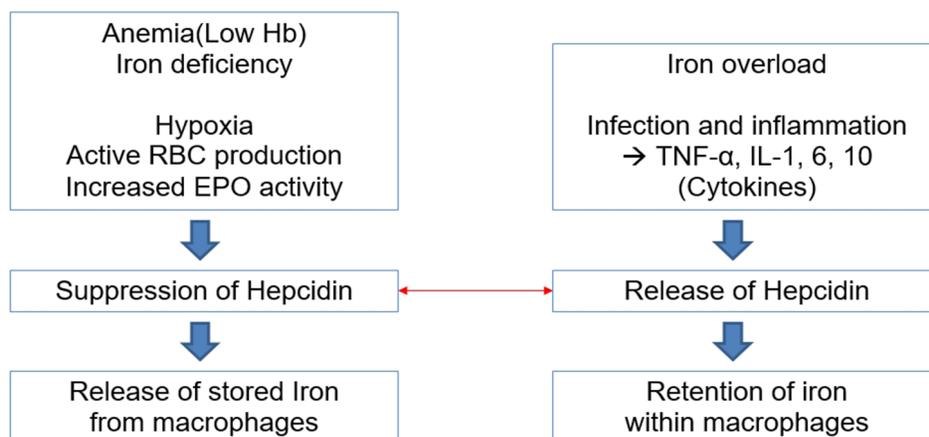


Fig. 1. Expression of hepcidin that is influenced by some physiological conditions. This figure shows two different expression of hepcidin getting influenced by some physiological conditions. Physiological conditions including anemia, active RBC producing state, iron deficiency and hypoxia suppress the hepcidin synthesis. This environment leads to the increased extracellular iron in the body for the iron homeostasis. In contrast, when there is overloaded iron or inflammation, hepcidin expression is increased.

suggested as the right dose of oral iron therapy for treating patients who have IDA, but recently giving iron every other day is recommended for better absorption of iron [23]. In a study, 90 octogenarian patients with IDA were randomly assigned to 3 groups with different dosages of elemental iron treatment: 15 mg, 50 mg, and 150 mg administered for 2 months. There was a significant increase in Hb levels (average was 1.3 g/dL) in all 3 groups without between-group differences, and lower dose groups resulted in fewer adverse events such as black stools. Therefore, this study demonstrated that low doses of iron supplements are effective in the elderly patients [24].

However, some patients may not respond to oral iron supplements or cannot tolerate the adverse gastrointestinal effects of oral iron [14]. In such cases, IV iron supplementation is needed. IV iron supplementation is also preferable for patients who have chronic kidney disease (CKD), who are pregnant, or who receive surgery because IV iron is more effective in treating anemia, thus decreasing the demand for allogeneic blood transfusion significantly [19,20]. In

addition, IV iron is better than oral iron in keeping postoperative Hb values higher and the duration of hospital stay shorter [17]. A recent RCT (2016) with 116 anemic patients who had nonmetastatic colorectal cancer found no significant difference between IV iron (FCM) and oral iron (ferrous sulfate) in reducing the need for blood transfusion. However, IV iron was better than oral iron for treating preoperative anemia and iron deficiency [25].

Table 1 shows different IV iron formulations. There are no published data about the benefit of one formulation over another, but between iron IV preparations there exist structural differences which might affect the total cost of treatment [26]. One RCT demonstrated that ferumoxytol and iron sucrose, 2 types of IV iron, showed similar rates of adverse events and similar effects on Hb increase; however, another RCT showed that ferumoxytol resulted in a greater increment in the Hb levels than iron sucrose did ($P=0.0124$) [27,28].

About 1,000–1,500 mg of iron is a standard dose for most surgical patients in practice [14]; to estimate *Total iron deficit (TID)* of

Table 1. Characteristics of different intravenous iron agents

	Brand Name (approval year, FDA)	Molecular Weight (kD)	Plasma half-life (hour)	Carbo-hydrate	Iron concentration (mg/mL)	Maximal single dose (mg)
FCM	Ferinject [®]	150	16	Carboxymaltose (branched polysaccharide)	50	20 mg/kg (max 1000 mg) in Europe 2 doses of 750 mg in the US
	Injectafer [®] (in the US, 2013)					
Iron gluconate	Ferrlecit [®] (1999)	289–440	1	Gluconate (monosaccharide)	12.5	125
Iron sucrose	Venofer [®] (in Europe & in the US, 2000)	30–60	6	Sucrose (disaccharide)	20	200
Ferumoxytol	Rienso [®] (in Europe)	750	15	Polyglucose sorbitol carboxy-methylether (branched polysaccharide)	30	510
	FeraHeme [®] (in the US, 2009)					
Iron isomaltoside 1000	Monofer [®] Monoferro [®]	150	20	Isomaltoside (linear Oligosaccharide)	100	20 mg/kg
LMW-ID	Cosmofer [®] (in Europe)	165	20	Dextran (branched polysaccharide)	50	20 mg/kg
	INFeD [®] (in the US, 1992)					
HMW-ID	Not available in Europe	265	60			
	Dexferrum [®] (in the US, 1996)					

FDA, food and drug administration; HMW-ID, high molecular weight iron dextran; LMW-ID, low molecular weight iron dextran.

patients, the modified Ganzoni formula can be used, which is $TID (mg) = 2.4 \times [target\ Hb - actual\ Hb (g/dL)] \times body\ weight (kg) + 500\ mg$ [7,29].

However, it was revealed that IV iron increases the risk of infection. This result is in contradiction to another meta-analysis (2014) including 2,658 dialysis patients with functional iron deficiency that demonstrated that IV iron did not increase infection risk [30]. Nevertheless, IV FCM can induce hypophosphatemia. The frequency of hypophosphatemia is much higher when using FCM than when using IV iron sucrose or iron isomaltoside 1000 [21]. Furthermore, there could be infrequent hypersensitivity reactions [7]. Therefore, it is essential to monitor patients precisely in a clinical setting when the IV iron supplementation is administered. However, in 2013, a study suggested that the advantages of using IV iron appropriately surpass the associated risks [3].

EPO THERAPY FOR PBM

Erythropoietin (EPO), mainly secreted by the adult kidney, is an essential regulator of RBC production. In Europe, recombinant human erythropoietin (rHuEPO) is allowed to be used to reduce rates of allogeneic blood transfusion for patients who are expected to undergo elective orthopedic surgery with moderate blood loss and have a Hb value between 10 and 13 g/dL and enough stored iron. In the US, the range of this indication is expanded to other non-cardiac, nonvascular elective surgeries [3]. One meta-analysis in 2016, including 7 studies (2,439), showed that there is a decreased chance to get allogeneic transfusions when EPO was used preoperatively for patients undergoing total hip arthroplasty (THA) and/or total knee arthroplasty (TKA) [31].

Moreover, using erythropoiesis-stimulating agents (ESAs) including EPO, rHuEPO, epoetin alfa, darbepoetin alfa, and continuous erythropoiesis receptor activator (CERA) together with iron therapy may be more effective. According to the Cochrane Database systematic review, the addition of iron supplementation to ESAs (compared with ESAs alone) proved to have a significantly positive effect on hematopoietic response in patients with chemotherapy-induced anemia ($P < 0.0001$) [32]. Iron supplementation with ESAs can be helpful in treating anemic patients with CKD or inflammatory bowel disease [19,33].

Patients who have Hb levels lower than 13 g/dL should start EPO therapy 1 month before surgery [29]. A recent review suggested that it is not standardized to use iron or EPO during the acute phase of critical illnesses. The limitation is because both iron and EPO management slowly affect RBC production and Hb level increases

during the acute phase of illnesses [34]. Steuber et al. [35] showed the expected time to have a peak effect in some iron and ESA agents to be 3–6 months for oral ferrous sulfate and 2–4 weeks for IV iron sucrose, FCM, and subcutaneous (SC) epoetin alfa. The approved dose of subcutaneous rHuEPO is 300 U/kg per day (10 days before surgery, on the day of surgery, and 4 days after surgery) or 600 U/kg per week (21, 14, 7 days prior to surgery, and on the day of surgery) [3].

However, NICE guidelines advised that it is dangerous to use EPO routinely, unless patients refuse blood transfusions or have RBC antibodies. The cost of EPO is high, and there are increased risks of thromboembolic events and tumor growth with accelerating angiogenesis [4]. According to a review of many studies, thromboembolic hazard of ESAs was mostly found in patients with CKD who had been treated with numerous doses of ESAs for a long time and in high risk populations such as critically ill and cancer patients [30], as opposed to the use of ESA in the preoperative setting, which typically involves much shorter duration of treatment and lower doses often used in combination with anticoagulants [30]. Nevertheless, thromboembolic episodes can be reduced through numerous measures. One of the most important measures is to ensure that the Hb concentration is not excessively high. Although the target Hb level has not been clearly defined yet, EPO injection must be stopped if the Hb value exceeds 15 g/dL in elective orthopedic surgery [29]. Another method is to administer IV iron with rHuEPO [3]. Preoperative administration of IV iron is recommended to avoid the risk of decreased iron stores caused by EPO therapy [7] since the iron deficiency is a cause of thrombocytosis that may lead to a high thromboembolic risk, especially in cancer patients [33]. The addition of oral iron can have cost-saving effects on EPO, which is discussed in the orthopedic surgery section later.

CLINICAL USE: CARDIAC SURGERY

Cardiothoracic surgery is one of the specialties requiring effective PBM. More than 30% of patients who undergo elective coronary artery bypass graft (CABG) need an allogeneic blood transfusion, and approximately 20% of total transfusions are related to the cardiac surgery [36]. After a blood conservation program in cardiac surgery was introduced in a community hospital, the transfusion rate fell to 10.6% as compared with 42.5% in other institutions without the program [2].

A single-center study reported that low dose of preoperatively administered IV rHuEPO improved erythropoiesis rapidly and increased Hb values of patients undergoing heart surgery [37]. Accord-

ing to a meta-analysis of 11 RCTs, administration of rHuEPO before cardiac surgery decreased the rate of allogeneic blood transfusions [38]. One randomized blind controlled study in 2010 also showed that 5 perioperative injections of rHuEPO reduced the requirements of allogeneic blood transfusions postoperatively in patients undergoing CABG [36]. In another RCT conducted in 2011, 74 preoperative anemic patients scheduled for valvular heart surgeries received IV rHuEPO and iron sucrose therapy 1 day before surgery. As a result, the requirement for pre- and postoperative transfusion was reduced significantly [39].

However, a randomized study in 2004 concluded that postoperative IV iron sucrose therapy did not increase Hb levels significantly after cardiac surgery [40]. An RCT by Garrido-Martin et al. [41] including 159 patients (2012) showed that IV or oral iron supplementation did not effectively correct anemia after cardiopulmonary bypass and did not decrease the need for blood transfusions. However, Johansson et al. [42] (2015) stated that Garrido-Martin et al.'s results

(2012) were due to lower doses of IV iron used in their trial. Also, Johansson et al. [42] (2015) demonstrated that the decrease in Hb values in the IV iron group was smaller than that of Hb levels in the placebo group. However, the need for blood transfusions and the rate of adverse events were similar between the two groups.

Gross et al. [43] (2015) analyzed a total of 2,662 patients undergoing cardiac surgeries including CABG and valve procedures and divided them into two groups, 387 before the PBM era (2006–2007) and 2,275 in the PBM era (2007–2012). Although the intervention in this study included not only preoperative IV iron and EPO, but also antifibrinolytics such as TXA, the study concluded that PBM in cardiac surgery reduced the length of hospital stay, perioperative loss of RBCs, and need for transfusions.

More studies are needed to evaluate iron and EPO treatment as a part of PBM strategies during cardiac surgery. Most studies have demonstrated that perioperative IV iron and rHuEPO are beneficial for cardiac surgical patients, although the results varied depending

Table 2. Iron and erythropoietin administration in cardiac surgery

Study	Population and surgery	Intervention	Outcomes
Yazicioglu et al. (2001) [37]	53 patients Elective on-pump CABG	(Preoperatively) IV rHuEPO 100 IU/kg, 4 days before surgery (n=25)	Hb level↑
Madi-Jebara et al. (2004) [40]	94 patients Elective cardiopulmonary bypass	(Postoperatively) IV iron sucrose 200 mg/day (n=30), SC rHuEPO 300 U/kg+IV iron sucrose 200 mg/day (n=33)	Transfusion need and Hb level: no benefits
Weltert et al. (2010) [36]	320 patients Off-pump CABG	(Perioperatively) SC rHuEPO 14,000 IU, 2 days and 1 day before surgery+8,000 IU, on the day of surgery, 1 and 2 days after surgery (n=158)	Transfusion need↓ Hb level↑
Yoo et al. (2011) [39]	74 patients On pump valvular heart surgery	(Preoperatively) IV rHuEPO 500IU/kg+IV iron sucrose 200 mg, 16–24 hours before surgery (n=37)	Transfusion need↓
Garrido-Martin et al. (2012) [41]	159 patients Cardiopulmonary bypass	(Perioperatively) IV iron sucrose 3 doses of 100 mg/day (n=54), Oral ferrous fumarate 1 pill (105 mg of iron)/day (n=53)	Transfusion need and Hb level: no benefits
Johansson et al. (2015) [42]	60 non-anemic patients Elective CABG and/or valvular heart surgery	(Perioperatively) IV iron isomaltoside 1000, 1000 mg (n=30)	Transfusion need: no difference Hb level↑
Gross et al. (2015) [43]	2,662 patients CABG and/or valvular heart surgery	(Perioperatively) SC epoetin alfa 600 U/kg+IV iron sucrose 3x200 mg doses and/or other PBM choices (n=2,275)	Length of hospital stay↓ Perioperative loss of RBCs↓ Transfusion needs↓ Acute kidney injury↓

on the dosing, injection route, types of surgery, and other interventions (Table 2). In addition, the Spanish consensus in 2013 suggests administration of postoperative IV iron for treatment of postoperative anemia after cardiac surgery (Grade 2C) [44]. Furthermore, a study introduced an index, called Percentage HEMatocrit VARIation (PHEVAR). The authors concluded that the index may be used as an objective quality index for PBM in cardiac surgery patients, i.e., the higher the index, the worse the outcome postoperatively [45]. Further studies would be necessary to see if the same results can be reproduced by others.

CLINICAL USE: ORTHOPEDIC SURGERY

There are many studies dealing with PBM in orthopedic surgery (Table 3). THA, TKA, and hip fracture repair surgery are the major orthopedic surgeries requiring approximately 8% of total transfused units [46]. The first published study on IV iron therapy in patients with hip fracture was conducted by Goodnough and Merkel in 1996, but the first studies (Cuenca et al.) containing considerable

study population were published in 2004 and 2005, respectively [47].

In a pilot study in 2004, 157 patients were categorized into 2 groups. Group II patients (n=55) undergoing pertrochanteric hip fracture (PHF) repair surgery received 100 mg of IV iron sucrose on the admission day and before the operation, while Group I patients (n=102) did not. This study reported that, in patients with PHF, preoperative IV iron management seemed to lower the need for blood transfusion and morbidity after surgery. However, the results were significant only when the patient's Hb level was higher than 12 g/dL at admission [48].

According to an RCT study of 200 elderly patients with hip fracture surgery conducted in 2011, IV iron administration resulted in requiring fewer transfusions, but the results were not statistically significant. However, a panel constituted by Network for Advancement of Transfusion Alternatives recommended perioperative IV iron therapy for patients with scheduled orthopedic surgery [47]. The Spanish consensus in 2013 recommends perioperative IV iron administration in anemic patients undergoing orthopedic surgery (Grade 2B) [44]. Muñoz et al. [49] (2014) conducted a meta-analysis

Table 3. Iron and erythropoietin administration in orthopedic surgery

Study	Population and Surgery	Intervention	Outcomes
Cuenca et al. (2004) [48]	157 patients older than 65 PHF repair surgery	(Preoperatively) IV iron sucrose 100 mg, 3 days prior to and on the day of surgery (Additional 100 mg if Hb<12 g/dL) (n=55)	Transfusion need↓ (Significant when Hb >12 g/dL) Postoperative morbidity↓
Serrano-Trenas et al. (2011) [47]	179 patients older than 65 Hip fracture surgery	(Preoperatively) IV iron sucrose 200 mg (n=20), 400 mg (n=63), 600 mg (n=16)	Transfusion need↓
Muñoz et al. (2014) [49]	2547 patients Elective PHF, subcapital hip fracture, TKA, THA	(Perioperatively) IV iron sucrose 100–200 mg, 3 times, very short term + (Postoperatively) IV FCM 600 mg (n=1,538) With or without SC rHuEPO 40,000 IU (if Preoperative Hb<13 g/dL)	Transfusion need↓ Length of hospital stay↓
So-Osman et al. (2014) [50]	683 patients (Hb level 10–13 g/dL) THA and/or TKA	(Preoperatively) SC EPO 40,000 U weekly and Ferrofumarate 200 mg, 3 times a day, for 3 weeks before surgery + SC EPO 40,000 U on the day of surgery (if Hb >15 g/dL, stop EPO) (n=339)	Transfusion rate↓ High cost↑
Petis et al. (2017) [52]	3435 patients THA or TKA	(Preoperatively, before PAC) 1) Oral ferrous gluconate (35 mg of iron) daily or 2) Oral ferrous fumarate (100 mg of iron) daily (n=2,088)	Transfusion need↓ Use of EPO and IV iron before surgery↓

that included 2,547 patients. They concluded that very short-term perioperative injection of IV iron reduced the blood transfusion requirements and length of hospital stay.

A randomized, multicenter study in 2014 involved 2,442 adult patients who were scheduled for THA or TKA surgery. They applied the restrictive transfusion policy (threshold of 8 g/dL) to all patients and concluded that EPO significantly contributed to reducing the number of transfusions [50]. In addition, according to French guidelines for blood transfusion in 2014, EPO usage for preoperative anemia is highly recommended for major orthopedic surgery [29]. Bedair et al. [51] (2015) showed that the preoperative use of erythropoietin alfa for THA and TKA surgical patients with Hb values lower than 13 g/dL is effective in decreasing the need for transfusions and increasing postoperative hematocrit values.

In addition, using IV FCM with EPO raises the pre- and postoperative Hb levels. Rineau et al. [29] (2017) modified the PBM protocol, so the target Hb level to discontinue EPO was higher than 13 g/dL rather than 15 g/dL. They administrated subcutaneous EPO twice, 4 weeks and 3 weeks before surgery, with intravenous FCM injection 3 weeks before surgery. If the Hb level was still lower than 13 g/dL, then the third EPO was injected 2 weeks before surgery. In conclusion, this report demonstrated that the use of this new protocol reduced the number of EPO injections needed but with no change in transfusion rates. Petis et al. [52] (2017) showed that preoperative oral iron supplementation, which was administrated before preadmission clinic (PAC) blood retraction in patients undergoing THA or TKA,

increased Hb and ferritin levels. It also reduced the need for transfusions and for preoperative EPO or IV iron therapies, which may lead to cost-saving effects. This implies that the high cost associated with the use of EPO can be decreased by using iron formulations.

Most studies confirmed that preoperative IV or oral iron therapy and EPO therapy, either in combination or separately, are effective in orthopedic surgery. Furthermore, postoperative IV iron management can also be helpful. In 2014, Bisbe et al. showed postoperative IV iron improved some quality of life (EQ-5D) scores such as *usual activity* and *anxiety/depression* through a randomized trial of TKA patients [53]. Khalafallah et al. [22] (2016) also demonstrated that postoperative IV FCM might be beneficial for the patients with functional iron deficiency anemia who undergo major orthopedic surgery.

CLINICAL USE: NEUROSURGERY

In this section, surgery for neurosurgical trauma such as traumatic brain injury (TBI) would be excluded.

There is a lack of data about blood transfusions for patients undergoing neurosurgery. Also, there is limited literature regarding the relationship between PBM and neurosurgery (Table 4). These could be partially explained by a transfusion rate of 1.7% during neurosurgery, which is substantially low compared to other surgeries [54].

Cohen et al. [6] (2017) mentioned that the efficacy of iron supplementation and ESA in cranial surgery had not been studied independently. They reported that blood transfusion significantly

Table 4. Iron and erythropoietin administration in neurosurgery

Study	Population and surgery	Intervention	Outcomes
Springborg et al. (2007) [58]	54 patients SAH surgery or Coiling	IV rHuEPO 500 IU/kg/day for three days (n=24)	Glasgow Outcome Scale: no difference
Kisilevsky et al. (2016) [55]	4 patients Spinal surgery for tumor resection	(Preoperatively) Oral ferrous fumarate 300 mg twice daily (n=3) IV iron sucrose 200 mg for the first dose+ 300 mg for subsequent doses (n=2) SC EPO 20,000 U/dose (≤65 kg) & 40,000 U/dose (>65 kg) (n=2) Other PBM strategies were used.	No severe perioperative anemia
Hardesty et al. (2017) [54]	136 patients Cranial and spinal surgery (Arteriovenous malformation, brain tumor, laminectomy, Anterior cervical discectomy and fusion, posterior spinal fusion)	(Perioperatively) EPO (n=4), Iron (n=1), with other PBM strategies (n=68)	Mortality, average blood loss, Intensive care unit stay: similar

increased the major morbidity risk and death within 30 days after surgery. Outcomes of neurosurgical patients can be worsened by both anemia and transfusion, while some other studies insist that increasing Hb levels higher than 11 g/dL through blood transfusion may be beneficial [54].

Although the data is derived from a single center with only 4 cases of spinal tumor resection surgery, Kisilevsky et al. [55] (2016) reported that patients who were treated with one or more PBM methods perioperatively were found not to have postoperative anemia or severe complications. The preoperative strategies were beneficial. However, antifibrinolytic agents were also used in these cases, so this study does not prove the advantages of iron supplementation and EPO management alone. In contrast, Hardesty et al. [54] (2017) compared 68 patients who refused blood transfusion with 68 control patients who accepted blood transfusion. The mortality, complications after surgery, duration of hospital stay, and readmission rates were similar in both patient groups. Other PBM modalities such as cell saver were also used intraoperatively in this study; therefore, it is hard to prove the efficacy of iron and EPO management independently.

Apart from PBM, EPO can be administered for another reason in neurosurgery. EPO acts not only during erythropoiesis but also against vasospasm during subarachnoid hemorrhage (SAH). That is, EPO also has neuroprotective activity in improving functional outcomes and preventing ischemic damage in the brain [56]. Additional detailed studies are necessary to prove the efficacy of iron and EPO administration in neurosurgery, especially considering EPO's neuroprotective role.

CONCLUSION AND PERSPECTIVES

This review included not only case studies but also meta-analysis, systemic reviews, and RCTs. Numerous meta-analyses and RCTs have demonstrated the efficacy of preoperative oral and IV iron and EPO, and recently postoperative iron usage in elective surgical patients. The most efficient way in each situation may vary depending on the patient's condition, surgery categories, doses of administered supplements, and other variables.

In most cases, IV iron is preferable to oral iron, and EPO is recommended for use in combination with IV iron. Perioperative IV iron and EPO therapy has been proved to be useful in cardiac and orthopedic surgery. However, in the department of neurosurgery, there is still a paucity of information about iron and EPO management.

In addition, there are increasing numbers of patients who undergo major urological surgery, and the reported prevalence of pre-

operative anemia associated with urological surgery is high, 39.7% in nephroureterectomy and 45% in radical cystectomy [57]. Accordingly, there is a need for future studies assessing the efficacy of iron and EPO therapy as well as other PBM modalities in urological operations.

In the near future, iron and EPO management for PBM may evolve into a more individualized system [4]. As PBM becomes essential and widely used, there is a need for multi-disciplinary cooperation involving surgeons, hematologists, anesthesiologists, and other physicians and technicians to use PBM effectively.

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