Role of Preoperative Intravenous Iron Therapy to Correct Anemia before Major Surgery

By
Abdelsalam M. Elhenawy

A thesis submitted in partial fulfillment of the requirements for the degree of

Master of Science

in

Clinical Epidemiology

Department of Public Health Sciences

University of Alberta

ABSTRACT

In patients undergoing elective major surgery, preoperative anemia is a common morbidity that may necessitate allogeneic blood transfusion in a substantial proportion of patients depending on the degree of anemia. Allogeneic blood transfusion has potential adverse outcomes. Preoperative intravenous iron (IV) monotherapy has been recommended as a bloodless therapy to decrease perioperative blood transfusion; however, class 1A evidence is lacking due to the absence of meta-analysis and systematic reviews, and high quality randomized controlled trials.

The aim was to evaluate the efficacy and safety of preoperative IV monotherapy injection versus placebo/oral iron (standard of care) as a strategy to increase the hemoglobin concentration to minimize the necessity of blood transfusion. Therefore, this systematic review and meta-analysis of the randomized controlled trials was conducted.

The results of the meta-analysis study in this thesis showed that preoperative IV iron supplementation was found to be effective in decreasing allogeneic blood transfusion by 17% in patients who received IV iron therapy compared to who did not receive it. This reduction in transfusion rate was statistically significant (risk ratio [RR]: 0.83, 95% confidence interval [CI]: 0.70, 0.98, p = 0.03). Concomitantly, pre-operative IV iron therapy was also associated with increases in the hemoglobin concentrations prior to surgery compared with not receiving pre-operative IV iron therapy (mean difference [MD] between the study groups: 6.65, 95% CI: 0.83, 12.47 g/L, p = 0.03). Because some of the trials started administration of IV iron 3-4 weeks before surgery and some studies started the IV injection 1-2 days before surgery, the hemoglobin rise showed a bi-phasic pattern with the first wave appeared before surgery and the second wave existed 4 weeks after

surgery. Moreover, the blood loss perioperatively interrupted this hemoglobin concentration growth throughout the hospital stay. As a follow-up > 4 weeks postoperatively, the second wave existed and the hemoglobin level increased significantly again in favor of the IV group (6.46, 95% CI: 3.11, 9.80 g/L, p = 0.0002) indicating an augmented/new effect of the injected IV iron later by the other trials.

Intravenous iron administration was able to restore the depleted iron stores and increased serum ferritin levels significantly pre-surgery, at hospital discharge, and > 4 weeks postoperatively, (MD between groups: 108.03, 95 % CI: 45.58, 170.49 ng/mL, p = 0.0007), (MD between groups: 547.77, 95 % CI: 36.61, 1058.94 ng/mL, p = 0.04), and (MD between groups: 391.00, 95 % CI: 271.44, 510.56 ng/mL, p < 0.00001), respectively. There were no differences in non-serious and serious adverse effects between the two groups (RR: 1.17, 95% CI: 0.80, 1.71, p = 0.42) and (RR: 0.89, 95% CI: 0.40, 1.99, p = 0.77) respectively.

Similar results were obtained from the case series of the thesis where is IV iron treatment was capable to increase Hb level significantly from 125.70 ± 11 g/L at baseline to be 132.30 ± 16 g/L at the time of surgery with p = 0.007, with mean difference of 6.6 g/L (95% confidence interval [CI]: 2.00, 11.11 g/L). Moreover, depleted iron stores were restored, and serum ferritin level increased significantly from 25.43 ± 18.47 ng/mL at baseline to be 239.80 ± 18.47 ng/ml at surgery (p = 0.004). Allogeneic perioperative red blood cell transfusion occurred in 9 (29%) patients, which is lower than a recent Canadian report.

Preoperative intravenous iron monotherapy is a safe and efficacious intervention. It successfully lowers the transfusion rate and increases hemoglobin concentration pre-

surgery and at four weeks postoperatively. However, further randomized controlled trials are required to establish its effectiveness, potential adverse effects, and to show which intravenous iron preparation has better cost-effectiveness than the other preparations to reduce blood transfusion.

PREFACE

This Master's Degree thesis is an original work by Abdelsalam Elhenawy. All data in Chapters III and VI were collected and synthesized by Dr. Elhenawy, with Dr. Meyer serving as an independent second reviewer. Abdelsalam Elhenawy wrote the thesis chapters and conducted the statistical analyses. This thesis is based on three papers written as Chapters II, III, and IV.

A version of the first paper (Chapter II) has been published as *Elhenawy AM, Meyer SR, Bagshaw SM, MacArthur RG, Carroll LJ. Role of preoperative intravenous iron therapy to correct anemia before major surgery: study protocol for systematic review and meta-analysis. Syst Rev. 2015 Mar 15; 4:29. doi: 10.1186/ s13643-015-0016-4.*

To achieve chapter IV *(Optimizing preoperative* hemoglobin *in adult cardiac surgery using intravenous iron sucrose (Venofer): a case series study),* on June 5, 2014, we obtained approval from my institutional review ethical board (REB #: Pro00045780) to waive the need for patient consent. A copy of this approval is the Appendix 6 of the thesis.

ACKNOWLEDGEMENT

The present work was carried out in the Clinical Epidemiology Program at the School of Public Health, University of Alberta. We as a group do not have any relevant/similar publications.

My first appreciation goes to my supervisory committee members, Dr. Steven Meyer, Dr. Linda Carroll, Dr. Sean Bagshaw, and Dr. Roderick MacArthur for their excellent mentorship, kindness, guidance, and valuable suggestions.

I wish to express my sincere thanks for Mrs. Trish Chatterley who is a Collections Manager at John W. Scott Health Sciences Library at the University of Alberta for her support in developing a search strategy for the planned systematic review and updating the search twice during my working on the systematic review and meta-analysis chapter of the thesis.

I would like to thank Mr. Ben Vandermeer; he is a biostatistician at the Alberta Research Centre for Health Evidence (ARCHE), located within the Department of Pediatrics at the University of Alberta for his guidance in using the RevMan statistical software.

My next appreciation goes to Mr. Imran Hassan, he is a statistician at the Epidemiology Coordinating Research (EPICOR) Centre, the University of Alberta for his assistance to estimate the mean and the standard deviation using the confidence interval, p-value, standard error, Z-score and the sample size when the included trials did not report these.

I am deeply thankful and indebted to my wife Omnia who had compromised a lot to support me every day of our married life and especially for being my rock through the worst financial situation I have been through when I was working on my Master Degree.

My gratitude also goes out to my daughter Laila Elhenawy who is a Bachelor Degree student in Psychology Department at the University of Alberta, and my son Mohamed. I am thankful for their help conducting the evidence table from the included trials as double checkers for the numbers to eliminate the human being errors in the meta-analysis section of my thesis. Mohamed had provided great assistance when it came to technology.

My last thanks goes to the statisticians who contributed to numerous videos on YouTube on conducting meta-analyses. These were very helpful in this work.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

List of Abbreviations

ABT	Allogeneic blood transfusion
ACD	Anemia of chronic disease
AVR	aortic valve replacement
CBC	Complete blood count
CI	Confidence interval
CVP	Central venous pressure
ECMO	Extracorporeal membrane oxygenation
EPO	Erythropoietin
Hb	Hemoglobin
HCT	Hematocrit
ICU	Intensive care unit
ID	Iron deficiency
IDA	Iron deficiency anemia
IV	Intravenous
MCH	Mean corpuscular Hb
MCV	Mean corpuscular volume
MD	Mean difference
MCID	Minimal clinical important difference
RBCS	Red blood cells
RCT	Randomized controlled trial
RCTs	Randomized clinical trials
rFVIIa	Recombinant factor VIIa

RR	Risk ratio
SMD	Standardized mean difference
sTfR	Serum transferrin receptor
TIBC	Total iron-binding capacity
TSAT	Transferrin saturation
UIBC	Unsaturated iron-binding capacity
UK	United Kingdom
US	United States
VADs	Ventricular assistance devices
WHO	World Health Organization

CHAPTER I: INTRODUCTION

1.1. EPIDEMIOLOGY OF ANEMIA

Anemia is the most frequent hematological disorder worldwide. In a developed nation such as the United States, approximately, one quarter of the population is affected by anemia [1]. It is one of the most common reasons for the medical visits [2, 3]. According to research conducted by the World Health Organization (WHO) [4], about one quarter of the world's population is anemic, with the highest prevalence (almost 50%) in preschool-age children and the lowest prevalence (approximately 13%) in men. Moreover, this prevalence is accompanied with regional discrepancies and it varies according to age, sex, and pregnancy status [4]. Globally, anemia is one of the leading causes of disability, illness, and death [5].

1.2. ANEMIA BASICS

The WHO has defined anemia as circulating hemoglobin (Hb) levels of less than 120 g/L in females and 130 g/L in males [6]. Diagnosis of anemia is based on laboratory values of Hb, hematocrit (Hct) and on age, gender, race, and altitude. Anemia is a medical condition that, in most cases, develops secondary to an underlying disease. Although anemia is a very common illness, it can easily be missed in clinical settings since many patients will not report anemia symptoms such as fatigue, unless specifically asked. Additionally, the symptoms of anemia are frequently vague, and the diagnosis is essentially laboratory based.

Etiologically, the main causes of anemia are nutritional deficiencies, chronic disease, blood loss, and, less frequently, hemolytic anemia [2]. The most common form of anemia is iron deficiency anemia (IDA) followed by anemia of chronic disease (ACD) [2].

1.3. CAUSES OF IRON DEFICIENCY ANEMIA

Iron is an essential constituent of diet, and without it, survival is not possible. It is a vital element for numerous metabolic processes required for the human cells to mature and multiply [7]. Iron is an essential component in heme and Hb structure to enable oxygen transport to all body cells [8]. Consequently, reduced iron consumption is one of the leading risk factors for global illness and mortality [9]. Surprisingly, iron is one of the naturally existing compounds found in the Earth's crust, and it is one of the most abundant elements worldwide. Despite this, only a minuscule quantity of iron exists as a constituent of living cells. This is because iron exists in oxidized and insoluble form making it less bioavailable [10]. The principal etiologies of IDA are due to insufficient dietary iron, poor iron bioavailability, disproportionate iron demands and blood loss [11]. Interestingly, the causes of IDA vary from one country to another and differ across socioeconomic status within the same country. Inadequate iron intake and parasitic infestations causing blood loss are the primary sources in low and middle-income countries [3]. In contrast, chronic blood loss as intestinal bleeding (including peptic ulcer, hiatal hernia, or colorectal tumors) is the leading cause in the industrialized countries population [3]. Interestingly, even within countries, additional variations in causes of IDA relate to age and gender. For example, in premenopausal women, menorrhagia and frequent menstruation are frequent causes of IDA [12].

1.3.1. Blood loss

To avoid IDA, the human body maintains a steady equilibrium between iron storage and loss. This is also necessary to achieve sufficient erythropoiesis [13]. To accomplish this balance, on a daily basis the body obtains about 20 mg of iron as a recycled iron from hemolyzed red blood cells (RBCs), and only 1-2 mg from intestinal dietary absorption; the total of these two amounts is sufficient to keep erythrocyte formation under normal conditions [12]. Under unusual conditions, as in acute bleeding, iron stocks will be exhausted and iron supplies from the diet and reprocessed RBCs will be not adequate to compensate the ensuing IDA [14]. In human adults, sudden exsanguination of about 35% of the total blood volume is sufficient to evacuate the iron reservoirs [15]. Consequently, this will delay new erythrocyte creation. With the conditions of chronic bleeding that commonly involve smaller volumes, the body response differs and ten mL, which is equivalent to five mg of iron daily, could result in IDA over time [16].

1.3.2. Deficient diet

In countries of low and middle-income status, individual income is a key determinant of the quality of nourishment. Consequently, insufficient iron intake resulting in IDA is very common due to starvation, food paucity, undernourishment, malnourishment or combination of these [3]. Iron deficiency anemia is also more prevalent in situations where the iron demand is higher, such as growing children, adolescents, and gravid females [3]. In developed countries, a diet deficient of red meat, such as a vegetarian diet, can be a cause of IDA [3].

1.4. EPIDEMIOLOGY AND MAGNITUDE OF IDA

Iron deficiency anemia is the type of anemia that remains a problem, even though it is readily detected and can be easily treated [15]. IDA is the most frequent category of anemia with microcytic morphology [2]. Moreover, IDA continues to be the most common type of anemia seen in clinical practice [11]. Based on WHO reports, IDA was the primary cause of mortality in 237,000 patients worldwide [9]. This mortality effect has a geographical distribution pattern where 45% of deaths were due to IDA in Southeast Asia followed by 31% in Africa, 9% in the Eastern Mediterranean, 7% in the Americas, 4% in the Western Pacific and the lowest was 3% in Europe [9]. This also could be inferred from the occurrence and distribution of anemia across the globe [17].

1.5. IRON SUPPLY AND DISTRIBUTION

To have a full understanding of the pathogenesis of IDA, a comprehension of iron metabolism is essential. This is because erythrocyte formation and iron metabolism are intricately connected. In the human body, iron is a crucial component to achieving diversity of cellular activities by being involved in Hb and certain enzymes necessary for energy production [18]. With minor exception, every living human cell consumes iron in essential biological activities [19-21]. Moreover, iron is a physiologically important component of various classes of proteins [14]. According to their amounts in the body, the most abundant protein class is the heme protein, which is an essential element of Hb and myoglobin [14]. The other three protein classes are in smaller quantities: proteins with linked binuclear iron center (diiron-carboxylate proteins), mononuclear non-heme

iron proteins and iron-sulfur cluster proteins that reside in the cytosol, nucleus and mitochondria [14].

1.5.1. Iron Recycling

As mentioned above, most of the daily iron supplies come from the old RBCs when they are taken out of the circulation and recovered through a process called iron recycling. This process is accomplished mostly by splenic and hepatic macrophages [22]. Macrophages are one of the mononuclear phagocyte system cells. It uses heme oxygenase-1which is an endoplasmic reticulum enzyme to split heme and releases the iron derivative into the circulation [23]. Because extra iron is harmful to the human body, its levels are adjusted through iron absorption and storage in a systematic manner [24].

1.5.2. Heme, Iron Toxicity, and Iron Storage

An elevated risk of colorectal cancer has been linked to excessive dietary heme as demonstrated by several meta-analyses [25-28]. Moreover, a recent case-control study [29] showed high ferritin, which is an indicator of excessive iron in the body is associated with atherosclerosis which ultimately leads to ischemic heart disease. In humans, ferritin and hemosiderin are the accumulated form of excessive iron [30]. This iron accumulation process occurs in the hepatocytes and serves as a mechanism to mitigate iron toxicity [31]. Hence, one of the essential functions of ferritin is to bind iron and to liberate it only when needed as one component of a sophisticated balance mechanism by which the body maintains the total iron within normal ranges. Another physiological role of ferritin is to be an acute phase reactant that rises with sepsis, toxicity, damage or acute inflammatory conditions [32]. In comparison, hemosiderin, which is also an iron-storage

compound that is composed of denatured ferritin and some cellular fragments, is a sluggish source of iron to the body when required [33].

1.5.3. Iron Excretion

In humans, the only physiologic processes that result in iron elimination are menses and pregnancy [34]. However, 1-2 mg of iron are eliminated daily through the cellular breakdown of skin and the intimal lining of different systems of the body [12, 30]. To control total body iron, the peptide hormone hepcidin regulates iron absorption and organization [35].

1.5.4. Systemic Iron Homeostasis

To recognize and to manage IDA accurately, it is important to understand iron homeostasis. Over the last decades, extensive research has been conducted on iron metabolism and pathophysiology, which has led to advances in understanding and treating of IDA [36]. To briefly summarize, systemic iron homeostasis is a process by which the body responds to changes in iron demand [37]. Hepcidin hormone is the main controller of iron hemostasis [37-39], accomplishing this task through controlling iron reprocessing, intestinal absorption, and mobilization to adjust serum iron concentration [35]. Hepcidin, like other hormones, has specific regulators. When there is excess iron and during acute inflammation, hepcidin secretion is increased [40], while augmented erythropoietic activity considerably diminishes hepcidin secretion [41].

1.5.5. Disorders of Iron Homeostasis

Iron deficiency anemia is a status in which the entire quantity of iron in the body declines to such an extent that iron stocks are entirely exhausted, and hemoglobinization of new erythrocytes is disturbed [42, 43]. Under normal conditions, daily erythropoiesis necessitates the availability of approximately 20–25 mg of iron [10]. Procurement of this iron quantity comes mostly from iron reprocessing, with 2 mg being procured through intestinal absorption [44]. Intuitively, the requirement for iron is greater than normal during gestation, childhood, adolescence, and when the body has excessive or prolonged bleeding. The normal intestinal absorption of iron is only between 1 and 2 mg per day, although intestinal iron absorption can reach 2-4 mg per day in those with iron deficit status [45]. Since this amount is small, a daily-prolonged blood loss volume of 10 mL (this is equivalent to 5 mg of iron) will surpass the ability to absorb iron, and there will be an ultimate progression into IDA [46, 47]. On the other hand, due to the lack of a physiological process to expel extra iron from the human body, iron overloads without treatment can cause vital organ dysfunction [48].

1.6. RECOGNIZING IDA ANEMIA

1.6.1. Clinical Diagnosis

The signs and symptoms of IDA are expressed according to the degree of deficiency, and those patients with mild to moderate degree of IDA may have no signs or symptoms [14]. Moreover, when the symptoms exist, they are broad-spectrum (easy fatigability, shortness of breath, chest pain, fast heartbeat, headache, or dizziness), and IDA is commonly overlooked in search of a clinical diagnosis [3].

1.6.2. Laboratory Diagnosis

Laboratory investigations are the cornerstone for the diagnosis of IDA, along with dietary, medical history and physical examination. Precise IDA diagnosis necessitates not only laboratory evidence of anemia but also a verification of reduced iron stores. The workup for distinguishing IDA requires multiple blood tests and additional diagnostic methods to identify the cause. Investigations should be individually tailored instead of requesting a long list of blood tests. This list includes but is not restricted to: complete blood count (CBC) including all the RBC indices, reticulocyte count, peripheral smear, serum ferritin, transferrin saturation (TSAT %) level and serum transferrin receptor (sTfR). The mere identification of IDA is not sufficient, and instead, the workup needs to continue until an underlying etiology is found. Again, some of these investigations are aimed at verifying the diagnosis and others are aimed at searching for an underlying disorder. Additional laboratory investigations like stool testing, incubated osmotic fragility testing, the amount of lead in tissue, and bone marrow aspiration may be requested to confirm different etiologies of IDA. Due to a wide range of etiologies, knowing the mean corpuscular volume (MCV) as one of the RBCs indices restricts the differential diagnosis of anemia and guides the clinician [49]. For example, having microcytosis usually limits the possibilities of the diagnosis in three common etiologies; iron deficiency (ID), anemia due to inflammation, or thalassemia [49] without missing the other less common causes; hereditary sideroblastic anemia, lead poisoning, Vitamin B6 (pyridoxine), or copper deficiency, which result in acquired sideroblastic anemia.

1.6.2.1. Complete Blood Count

Complete Blood Count is a routine investigation ordered in patients with a broad range of presentation. Decreased Hb or Hct values guide the physician to investigate further. Additional information obtained from CBC report is the MCV (also called mean cell volume). MCV indicates the average size of the red blood cells (RBC) [50], whereas the mean corpuscular Hb (MCH) expresses the average amount of Hb per the RBC and the Mean corpuscular Hb concentration (MCHC) expresses the mean concentration of Hb per unit volume of red blood cells [50]. MCV, MCH and MCHC are very helpful to diagnose IDA (their normal reference range is: 75-95 fL, 27-31 pg/cell [50], and 32-36 g/dL respectively) [51].

1.6.2.2. Other Blood Tests:

Because ID is one cause of hypochromic microcytic anemia, doing many blood tests are helpful in making a differential diagnosis. Decreased serum level of ferritin; low serum iron; low TSAT% (<20%) [42] associated with increased level of sTfR and total iron-binding capacity (TIBC) are diagnostic for IDA [52]. By far, the most accurate test for ID is bone marrow aspiration; unfortunately, it is an invasive procedure [53]. However, ferritin concentration in blood reflects the human iron stores in the body and is the most efficient, simple and quick single test to diagnose ID [54] or iron overload [55]; values below 15 µg/L confirm ID whereas values greater than 100 µg/L usually exclude IDA [56]. However, with an inflammatory condition, ferritin as an acute phase reactant, its level may be normal or even high [42]. Therefore, it is important to emphasize that combining several parameters of iron status is better than a single test for accurate IDA diagnosis [53] particularly in patients with concomitant diseases.

1.7. PREOPERATIVE ANEMIA

1.7.1. Identifying the problem

Fundamentally, pre-existing anemia is the most frequent hematological preoperative abnormality among the patients experiencing major elective surgery [57]. In most cases, it is not detected beforehand, and instead is usually identified during standard preoperative laboratory evaluation [58]. It has been shown that, overall, about one-third of the entire patients undertaking elective surgery are anemic [59]. However, the prevalence of anemia can vary from 5% to 75% according to the operation needed, the population studied and patient vulnerabilities [60]. The highest prevalence of preoperative anemia (75%) was reported in those patients undergoing colectomy for advanced colon malignancy [61]. For cardiac surgeries, the occurrence of preoperative anemia ranges between 30% in isolated coronary bypass surgery [62] and 52% in cardiac surgery for rheumatic heart disease [63]. Preoperative anemia is more common in older patients than in younger patients [64-66]. Preoperative anemia is also more frequent among patients who have ischemic heart disease [64-66], and long-lasting diseases like diabetes mellitus, heart failure, chronic kidney disease, primary hematologic disorders, and other inflammatory diseases [67]. Generally, given similar amounts of perioperative blood loss, female patients are more susceptible to develop anemia because their circulating blood volume is relatively small compared to male patients [68].

Preoperative anemia, like anemia in general, has many etiologies, however, the IDA is the most common cause followed by ACD [69, 70]. In general, they are four categories of causes contributing in the etiology of preoperative anemia [71]: (i) associated malnutrition or impaired absorption can result in deficiencies in the essential

elements for the erythropoiesis like iron, vitamin B_{12}, folic acid, and proteins; (ii) concomitant status of increased inflammatory mediators that activate the immune system resulting in decreased iron availability and decreased erythropoietin production by the kidney; (iii) blood loss related to phlebotomies, bleeding, and hemolysis; and (iv) drug-induced as chemotherapy, angiotensin-converting enzyme inhibitors, metformin, and proton pump inhibitors.

Therefore, after preoperative anemia diagnosis, identification of the underlying etiology is also crucial to achieving the appropriate treatment for every patient. In fact, being scheduled for an elective surgery gives ample time for anemia correction [58] to improve the patient's condition [59]. Having said that, anemia management before surgery is not a priority for most of the surgeons [72].

1.7.2. Epidemiology of Blood Transfusion and Outcomes

Preoperative anemia is associated with a higher incidence of poor clinical outcomes [73-81], including higher mortality incidence in the first 30 days after surgery [73-77, 80, 81]. Furthermore, other studies have shown that preoperative anemia is independently associated with perioperative ABT and poor postoperative outcomes [78] including transfusion-related acute lung injury (TRALI) [82]; more graft occlusion post-coronary artery bypass grafting (CABG) [83]; nosocomial infections [84]; acute kidney injury, myocardial and neurological function impairment [85]; tumor recurrence [86]; and compromised immune function [87]. Therefore, the results of these studies suggest the need for adopting new blood conservation modalities to avoid preventable blood transfusions and its subsequent complications and additional cost.

Cardiac surgery is the biggest consumer for the blood and blood product, followed by orthopedic surgery during the perioperative period [88]. This might be related to blood loss, open heart-induced hemodilution, and coagulopathy that require transfusion [89]. However, a recent report from the Society of Thoracic Surgeons Adult Cardiac Surgery Database showed that transfusion due to preoperative anemia is associated with adverse outcomes in cardiac surgery [62].

Nonetheless, a consistent method for preoperative anemia patients' management has not been established yet. Nevertheless, allogeneic blood transfusion (ABT) does not mitigate the negative impact of preoperative anemia [75]. One large and recent study of patients undergoing non-cardiac surgery reported that the vast majority (94.9%) did not receive blood transfusions during surgery [80]. However, in those who did receive blood transfusions during surgery, even a minimal transfusion of one unit of RBCs was associated with increased mortality, severe morbidity and increased hospital resources consumption rate. Moreover, the incidence of poor outcome after transfusion during surgery was dose-dependent. Although it could be argued that the patients receiving blood transfusions during surgery were more likely to experience adverse outcomes anyway, the analysis in that study used propensity matching [80] which strengthens the confidence that the blood transfusion was a key determinant in the poor outcomes.

1.7.3. Strategies for perioperative blood conservation

For preoperative anemia to be managed accurately, it necessitates screening in advance to identify who is anemic, establishing the kind of anemia and starting the treatment a while before surgery [90]. Currently, a variety of drug therapy and non-

pharmacologic strategies [90] to conserve blood perioperatively has been suggested to diminish ABT (Table 1 in Chapter II). According to a propensity-matched analysis study of 322 Jehovah's Witness (JW) patients (who refuse blood product transfusions for religious reasons) undergoing cardiac operations, the JW patients had an equivalent long-term survival, better postoperative results, and shorter intensive care unit (ICU) lengths of stay compared to non-JW patients [91]. This suggests that, in many instances, ABT can be avoided. This idea has support from a recent meta-analysis of randomized controlled trials (RCTs), which found that when hospital policies restricting transfusions are in place, there is a lower risk of healthcare-associated infection in hospitalized patients [92].

Over the last two decades, correcting preoperative anemia using drug therapy has been suggested as a new modality to reduce perioperative ABT [93, 94]. Intravenous (IV) iron is one such drug therapy to be proposed to correct anemia and to lessen ABT [95]. It has higher adherence and acceptance by the patient than oral iron [95]. Moreover, in a post-partum hemorrhage IDA study trial, IV iron administration has shown to result in a more rapid increase in ferritin and Hb levels than oral iron [96]. In the surgical setting, the evidence mostly came from observational studies recommending preoperative IV iron therapy as an effective modality to raise serum Hb and to decrease ABT perioperatively [75, 97].

To date, proactive IV iron injection to correct preoperative anemia lacks evidence for standard clinical practice guidelines regarding who is a good candidate patient for treatment, which IV iron preparation is optimal, the dose and the best timing of therapy.

1.7.4. Solving the preoperative anemia problem

In this work, my goal was to answer the clinical question: Is preoperative injection of intravenous iron a safe and effective treatment to increase Hb and minimize allogeneic blood transfusion?

The next two chapters are concerned with a systematic review and meta-analysis of studies on the efficacy and safety of IV iron therapy in the preoperative setting to correct anemia, to reduce ABT transfusions, and to improve outcome. Chapter II consists of the systematic review protocol, published in Systematic Reviews, and Chapter III consists of the systematic review and meta-analysis.

CHAPTER II: INTRAVENOUS IRON THERAPY TO CORRECT ANEMIA BEFORE MAJOR SURGERY: STUDY PROTOCOL FOR SYSTEMATIC REVIEW AND META-ANALYSIS

Abdelsalam M. Elhenawy, Steven R. Meyer, Sean M. Bagshaw, Roderick G. MacArthur, Linda J. Carroll. Syst Rev. 2015 Mar 15; 4:29. doi: 10.1186/s13643-015-0016-4.

2.1. ABSTRACT

2.1.1. Background

Preoperative anemia is a common and potentially serious hematological problem in elective surgery and increases the risk for perioperative red blood cell (RBC) transfusion. Transfusion is associated with postoperative morbidity and mortality. Preoperative intravenous (IV) iron therapy has been proposed as an intervention to reduce perioperative transfusion; however, studies are generally small, limited, and inconclusive.

2.1.2. Methods/design

We proposed performing a systematic review and meta-analysis. We will search MEDLINE, EMBASE, EBM Reviews, Cochrane-controlled trial registry, Scopus, registries of health technology assessment, and clinical trials, Web of Science, ProQuest Dissertations and Theses, and conference proceedings in transfusion, hematology, and surgery. We will contact our study drug manufacturer for unpublished trials. Titles and

abstracts will be identified and assessed by two reviewers for potential relevance. Eligible studies are randomized or quasi-randomized clinical trials comparing the preoperative administration of IV iron with placebo or standard of care (oral iron) to reduce perioperative blood transfusion in anemic patients undergoing major surgery. Screening, data extraction, and quality appraisal will be conducted independently by two authors. Data will be presented in evidence tables and in meta-analytic forest plots. Primary efficacy outcomes are the change in hemoglobin concentration and proportion of patients requiring RBC transfusion. Secondary outcomes include the number of units of blood or blood products transfused perioperatively, transfusion-related acute lung injury, adverse events, postoperative infections, cardiopulmonary complications, intensive care unit (ICU) admission/readmission, length of hospital stay, and mortality. Dichotomous outcomes will be reported as pooled relative risks and 95% confidence intervals. Continuous outcomes will be reported using calculated weighted mean differences. Meta-regression will be performed to evaluate the impact of potential confounding variables on study effect estimates.

2.1.3. Discussion

Reducing unnecessary RBC transfusions in perioperative medicine is a clinical priority. This involves the identification of patients at risk of receiving transfusions along with blood conservation strategies. Of potential pharmacological blood conservation strategies, IV iron is a compelling intervention to treat preoperative anemia; however, existing data are uncertain. We propose performing a systematic review and meta-

analysis evaluating the efficacy and safety of IV iron administration to anemic patients undergoing major surgery to reduce transfusion and perioperative morbidity and mortality.

Systematic review registration

PROSPERO CRD42015016771

http://www.crd.york.ac.uk/PROSPERO/display_record.asp?ID=CRD42015016771#.VPkN3fnF-YM

Keywords: Intravenous iron therapy; Preoperative anemia; Major surgery

2.2. BACKGROUND

2.2.1. Epidemiology of preoperative anemia

Anemia is defined by the World Health Organization (WHO) as a hemoglobin (Hb) concentration less than 130 g/L in men and 120 g/L in women [6]. Preoperative anemia is the most common hematological abnormality among the patients undergoing major elective surgery [57]. The prevalence of preoperative anemia ranges from 5% to 75%, depending on patient susceptibilities and the proposed surgical procedure [60]. Preoperative anemia is more common among older patients and those with chronic diseases such as heart failure, diabetes mellitus, chronic kidney disease, primary hematologic diseases, other inflammatory diseases [67], and coronary artery disease [64, 65]. Although diagnosis and treatment of anemia preoperatively are essential to optimize the patient's condition [59], preoperative anemia management is not a priority for most surgeons [72].

2.2.2. Epidemiology of blood transfusion and outcomes

Preoperative anemia has been associated with an increased risk for 30-day mortality [72, 80]. Preoperative anemia has also been shown to be an independent risk factor for perioperative red blood cell (RBC) transfusion and for postoperative morbidity [78]. Major morbid outcomes include transfusion-related acute lung injury (TRALI) [82], nosocomial infections [84], increased graft occlusion after coronary artery bypass grafting (CABG) [82], myocardial events, neurological events, acute kidney injury [85], tumor recurrence [86], and suppressed immune function [87]. In a recent large study of 22,785 consecutive patients, investigators found that transfusing as little as 1 or 2 units of RBCs was associated with increased morbidity and mortality after cardiac surgery [98] supporting a previous systematic review of observational studies [99]. The findings from these studies would imply that strategies to reduce unnecessary RBC transfusions might be associated with improved postoperative outcomes. RBC transfusions are also associated with significant cost related both to the product itself and the morbid events associated with unnecessary RBC transfusions that contribute to additional direct and indirect hospitalization cost [100]. In a recent RBC transfusion cost analysis study, the actual cost for each RBC unit was reported to range between US $522 and US $1,183 after calculating the direct and indirect costs, which include consumables, laboratory testing, nursing time, patient transport, treatment costs, and staff fees resulting in increased cumulative total cost [101]. This is substantially higher than previous estimates of the cost of each RBC unit at US $250 to US $550 [102].

National US data [103] showed a decline in blood transfusion usage estimate by 3% over each of the 2 years (2009 to 2010), and similar data [104] have been reported in the UK as well. Although many therapeutic modalities have been initiated to minimize the

patients' requirement for perioperative RBC transfusion, the rate of transfusion remains unacceptably high and variable across both cardiac (17 to 80%) [105, 106] and non-cardiac major surgery [107]. These observations would imply that transfusion practices are variable across the patient, healthcare provider, and health system factors. This may stem from the absence of high-quality evidence to guide the management of perioperative anemia and blood conservation.

2.2.3. Strategies for perioperative blood conservation

A variety of contemporary perioperative pharmacologic and non-pharmacologic blood conservation strategies (Table 1) [87] have been proposed and variably adopted to minimize RBC transfusion. In a recent study, the outcomes of 322 Jehovah's Witness (JW) patients undergoing cardiac surgery, who, for personal beliefs, refuse transfusion of all blood products including RBCs, were evaluated. In this study, JW patients had comparable long-term survival to those willing to receive RBC transfusion in a propensity-matched analysis; however, JW patients had fewer postoperative complications and shorter intensive care unit (ICU) lengths of stay [91]. These provocative findings would imply that many RBC transfusions might be unnecessary. In fact, these data suggest that blood conservation strategies, including preoperative treatment of anemia, may either reduce exposure to RBC transfusions or even act as a trigger for RBC transfusion. In addition, a more recent meta-analysis of randomized trials with 8,735 patients showed a lower risk of healthcare-associated infection for a restrictive RBC transfusion strategy in comparison to a liberal transfusion strategy in hospitalized patients [92].

Table 1: Current strategies for perioperative blood conservation

Conservation strategy	*Examples*
1. Pharmacological therapies	a. Antifibrinolytic drugs (aprotinin, tranexamic acid, epsilon-aminocaproic acid)
	b. Desmopressin acetate
	c. Recombinant factor VIIa (rFVIIa)
	d. Erythropoietin (EPO)
	e. Topical hemostatic agents
2. Autologous blood transfusion	a. Preoperative autologous blood donation
	b. Acute normovolemic hemodilution
	c. Red cell salvage (intraoperative and postoperative)
3. Anesthetic techniques	a. Controlled hypotension
	b. Spinal or epidural anesthesia
	c. Central venous pressure (CVP) manipulation
4. Surgical techniques	a. Coagulation diathermy devices, lasers, and ultrasonic scalpels
	b. Minimally invasive surgery
	c. Endoscopic and laparoscopic surgery
5. Blood substitutes	a. Solutions of modified hemoglobin
	b. Perfluorocarbon emulsions
6. Transfusion protocols, guidelines, and clinical audit	

2.2.4. Preoperative intervention: prophylactic iron therapy

Preoperative pharmacologic treatment of anemia has been proposed to reduce perioperative RBC transfusion [93, 94]. One potential strategy is the use of intravenous (IV) iron. Iron is fundamental in RBC formation and is the most common nutritional

deficiency in both developed and developing countries [108]. A recent study [109] reported that usage of oral iron to treat iron deficiency anemia (IDA) is limited by gastrointestinal absorption, particularly, in the patients with associated acute or chronic diseases [110]. IV iron has been reported to increase the hemoglobin (Hb) level and to replenish iron stores more rapidly than oral iron formulation in women with post-partum IDA in a variety of randomized controlled trial (RCT) studies in other areas of medicine such as post-partum hemorrhage [96], but in surgery, most have been observational in nature. Consequently, preoperative IV iron has been proposed as an efficacious strategy to increase serum Hb and minimize exposure to perioperative RBC transfusions [97, 111]. To date, there is no broad consensus or established clinical practice guideline to support the routine use of prophylactic IV iron to treat anemia before major elective surgery. Moreover, additional questions about the optimal timing of therapy, dose of iron, and whether anemic patients need additional nutritional supplementation have yet to be answered. However, there are a few guidelines recommending the use of IV iron for anemia in surgical cases, but all are lacking class 1A evidence-based medicine [112-114]. To date, there are relatively few studies, the majority of which have been small and non-definitive, those have evaluated the efficacy and safety of IV iron preparations in patients undergoing major elective surgery. A recent meta-analysis [115] showed that very low-quality evidence of IV iron results in modest increases in Hb levels compared with oral iron or inactive control, but without clinical benefit. Unfortunately, this meta-analysis was less homogeneous than would be ideal, and they were not able to do subgroup analyses for different types of participants (blood loss, cancer, preoperative anemia, chronic heart failure, autoimmune disorders, and infectious disease). In addition,

their literature search ended July 2013. Three other recent studies have been published as well. The first is a systematic review for RCTs with restricted language and search time frame [116], the second is a systematic review and meta-analysis for RCTs restricted to colorectal surgery [117], and the third is a systematic literature review of RCTs and observational studies restricted to cardiac surgery [118]. All three failed to find a sufficient evidence to support the use of IV iron to decrease RBC transfusion. Accordingly, we propose to perform a systematic review and evidence synthesis on the efficacy and safety of IV iron therapy in the preoperative setting to treat anemia, reduce transfusions, and improve outcome. This review will capture recently published RCT studies, will include a broad range of elective surgery, and will not be limited to English publications.

Hypothesis

We hypothesize preoperative IV iron therapy will improve preoperative Hb concentrations in anemic patients undergoing major elective surgery, reduce the need for RBC transfusion, and reduce complications compared with placebo or oral iron as the standard of care. We will synthesize the available data on the efficacy and safety of IV iron therapy to increase Hb levels, avoid transfusions, and improve outcomes for anemic patients undergoing major elective surgery.

Objectives

To perform a systematic review and evidence synthesis of all randomized and quasi-randomized studies investigating (a) the efficacy of IV iron administration to improve preoperative Hb concentration and reduce RBC transfusion rate, (b) the safety

of IV iron formulations with respect to adverse effects, and (c) the effectiveness of IV iron administration to reduce perioperative major morbidity and health resource use.

2.3. METHODS/DESIGN

2.3.1. Search strategy

In consultation with a health sciences librarian at the John W. Scott Health Sciences Library at the University of Alberta, we will search MEDLINE, EMBASE, EBM Reviews, and the Cochrane-controlled trial registry in the Cochrane Library, Scopus, registries of health technology assessment and clinical trials, and Web of Science. We will search the literature using the following search terms: iron or dextran or Venofer or ferric or ferrous or ferrlecit AND anemi* or anaemi* AND preoperat* or postoperat* or perioperat* or operati* or surg* or presurg* or postsurg* or perisurg* AND random* or trial or placebo*. An example of the search conducted in MEDLINE is in Appendix 1. In addition, we will contact our study drug manufacturer for unpublished trials, and we will search the ProQuest Dissertations and Theses database. Selected conference proceedings in transfusion, hematology, and surgery will also be searched. We will start from the earliest retrievable date of each database to February 2015, supplemented by a manual search of reference lists of retrieved trials. In addition, reference lists of prior reviews of similar topics will be searched for relevant studies. Language will be unrestricted.

2.3.2. Inclusion criteria

All the included articles must fulfill these criteria:

▪ Designs included are randomized and quasi-randomized studies in all different phases.

▪ Study compares any type of IV iron administered preoperatively to placebo or standard of care (oral iron).

▪ Study reports findings specific to adult humans.

▪ Study of patients undergoing any elective major surgery (Appendix 2) including, but not limited to, cardiac, thoracic, orthopedic, gastrointestinal, brain, urological, or obstetric operations

▪ Study patients have pre-treatment Hb level less than 120 g/L.

▪ Study reports at least one of the two following outcomes: absolute or relative change in preoperative Hb level and/or the proportion of patients receiving perioperative allogeneic RBC transfusion.

2.3.3. Exclusion criteria

Anyone of these criteria will result in a study being excluded:

▪ Observational (non-experimental) studies, reviews, opinion papers, letters to the editor, and studies with no reported methodology.

▪ Studies with no adult-specific findings.

▪ Studies involving patients with pre-treatment Hb level greater than 120 g/L.

▪ Studies using oral iron only.

▪ Studies using IV iron plus erythropoietin (EPO).

▪ Studies of minimally invasive robotic and laparoscopic surgery.

2.3.4. Primary outcomes

Primary outcomes:

▪ Absolute and relative change in preoperative Hb concentration.

▪ Proportion of anemic patients who received allogeneic RBC transfusion at any time perioperatively.

2.3.5. Secondary outcomes

These will focus mainly on safety-related outcomes:

▪ Total number of units of blood or blood products transfused perioperatively.

▪ All-cause mortality.

▪ Postoperative nosocomial infection (Appendix 2).

▪ TRALI (Appendix 2).

▪ Any reported reaction or side effect (Appendix 2) from receiving an RBC transfusion.

These may include, but are not limited to, hemolysis of transfused red cells, alloimmunization, development of antibodies against platelets or white blood cells, post-transfusion purpura, graft vs. host disease, infection; immunomodulation, and iron overload.

2.3.6. Study screening

Two authors (AE and SM) will initially review titles and abstracts to retrieve potentially relevant studies. Retrieved studies will then be subjected to the second phase of screening for eligibility, as determined by the eligibility criteria listed above. Reason(s) for ineligibility will be documented for all studies excluded in the second phase of screening, using pre-piloted forms. Disagreements will be solved through discussion or

by a third reviewer (SB) if necessary. We will provide the PRISMA study flow chart (Appendix 3).

2.3.7. Data abstraction

Data will be abstracted from the reports of all the included studies in duplicate and independently by two reviewers (AE and SM) on standardized and pre-piloted data extraction forms (Appendix 4). For the studies evaluating multiple treatment arms, comparisons will be made between IV iron arm and oral iron as the standard of care or placebo arm only. Discrepancies in extracted data will be agreed by consensus or involving a third author (SB) where consensus cannot be reached. Abstracted data from each study will include the details on the following:

• Study design, methodology, analysis, funding source, trial registration, and publication details.

• Aggregate participant demographic characteristics (for example, age, sex, and race).

• Aggregate participant characteristics including comorbid diseases and risk factors for anemia (for example, diet, any cause of blood loss, chronic or serious illnesses or infections, a family history of anemia, reasons/indications for major surgery).

• Dosage of drug administered, frequency, and duration of use.

• Hematocrit monitoring.

• Iron-related blood tests including serum iron, ferritin, transferrin, total iron-binding capacity (TIBC), transferrin saturation (iron saturation of transferrin), and unsaturated iron-binding capacity (UIBC).

• All primary and secondary outcomes reported.

• Study quality features (see below).

2.3.8 Assessment of methodological quality

To evaluate the risk of bias in both RCTs and quasi-randomized trials, two independent reviewers will use the Cochrane Collaboration's tool for assessing the risk of bias. This tool provides a model to assess the following domains of bias: random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incompleteness of outcome data (attrition bias), blinding of outcome assessment (performance and detection bias), selective outcome reporting (reporting bias), and a priori-derived sample size calculations. Each domain for each trial will have a ranking of "low," "unclear," or "high" risk of bias, in accordance with the Cochrane Collaboration's approach (Appendix 5) [116].

2.4. STUDY SYNTHESIS PLAN

2.4.1. Analysis plan

We will report the results of our search in a PRISMA flow chart, including the number of randomized and quasi-randomized studies (with their citations), the number of phases I, II, and III trials, and the number addressing our primary and secondary outcomes and language of studies. We will present tables outlining a) each study's characteristics, b) risk of bias for each study, and c) study results. Randomized studies and quasi-randomized studies will be presented in separate tables, and within each set of tables, there will be further stratification by a) outcome addressed (primary versus secondary), b) study phase, and c) high, medium, and low risk of bias. This information

will also be summarized in the text and the main biases identified for each study design and outcome.

The tables describing study characteristics will include information abstracted from the studies as per the data abstraction section above. A separate table will report each study's effect measures (findings) corresponding to our primary and secondary outcomes as follows: risk ratios (and their 95% confidence intervals) reflecting the association between preoperative IV iron administration and need for RBC transfusion, differences in change in Hb concentration (and statistical significant of this difference) between those who do and do not receive IV iron, proportion and pooled relative risk (RR) of unplanned ICU admissions and of ICU readmissions in each group, differences in hospital length of stay, and 30-day mortality in each group.

2.4.2. Meta-analysis

We will examine clinical homogeneity of the studies first, followed by an assessment of statistical homogeneity by using Cochrane's Q test and I^2 statistics, with $I^2 > 40\%$ considered significant heterogeneity [119]. We anticipate that there will be sufficient homogeneity across studies to justify a pooled statistical synthesis; however, we will conduct a qualitative synthesis if there is statistical heterogeneity. We consider the factors listed below as potential sources of heterogeneity in studies. Data from all trials fulfilling the eligibility criteria will be pooled for meta-analysis using a random effects model to accommodate the anticipated heterogeneity among study results and assuming that the individual specific effects are uncorrelated to the exposure variables [120]. Weights will be assigned to reflect sample size differences. For continuous outcomes

(change in Hb concentration, the number of transfused RBC among those transfused, ICU, and hospital lengths of stay), we will calculate the standardized mean difference (SMD) and test for group differences using unpaired t-tests or Mann-Whitney U test as appropriate with P-value < 0.05 signifying statistical significance. The SMD is used as a summary effect size, anticipating the included trials all assessing the same outcome. For categorical outcomes (nosocomial infection, TRALI, adverse reactions, ICU admission, and readmission), we will calculate pooled RR with 95% confidence intervals. Where studies reported the length of stay and 30-day mortality using the time to event analyses, we will calculate pooled hazard ratios with 95% confidence intervals. The meta-analysis will be performed in RevMan Version 5.3 software [121] and Stata V.13 (STATA Corp, College Station, TX, USA) [120].

2.4.3. Sensitivity analysis, subgroup analysis, and meta-regression analysis

We will conduct sensitivity analyses to assess the impact of each trial on the overall results and to examine whether an individual study is over-influencing the meta-analysis result. We will do additional sensitivity analyses by excluding studies with unclear or inadequate randomization. With the availability of at least three trials, we will conduct the following subgroup analyses to explore heterogeneity and to assess the robustness of our results:

1. Cardiac versus non-cardiac;
2. Different IV iron preparations;
3. Hb level trials with a mean equal to or greater than 10 g/dL;
4. Age studies with a mean age over the age of 65;

5. Excluding studies considered at high risk of bias according to the Cochrane risk of bias tool.

Our ability to conduct this subgroup analysis will depend on the information provided in the relevant studies. We will use univariable and bivariable meta-regression analyses to explore the impact of the following variables in each study on the pooled effect estimates for the primary outcome: age, sex, baseline ferritin level, baseline Hb level, baseline hematocrit value, total IV iron dose administered, and the rate of patients requiring allogeneic blood transfusion during or after the surgery. The effect of each variable on the pooled effect size will be considered significant when the P-value of the change in the effect estimate is less than 0.05 or when the 95% confidence intervals of the two analyses do not overlap.

2.4.4. Assessment of publication biases

To identify possible publication bias, we will construct a funnel plot of effect size against the inverse of standard error in the studies. Deviation from this funnel may suggest publication bias [122].

2.4.5. Grading the strength of the evidence

We will assess the overall quality of the evidence for each outcome in the included trials using the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) approach [123].

Ethical issues

For our meta-analysis, we will not require a health research ethics board review as all data will be sourced from existing literature.

2.5. DISCUSSION

Anemia is common in patients undergoing major surgery [57]. Over the past two decades, a variety of contemporary pharmacologic blood conservation strategies have been adopted to address preoperative anemia in attempts to minimize unnecessary RBC transfusion. However, the optimal treatment is not yet known due to the paucity of the randomized trials, most of which are small and have negative results, which may be a result of being underpowered to detect a treatment effect. Consequently, current knowledge implementation has been suboptimal, and there are no high-quality available clinical practice guidelines to inform best practice. A meta-analysis conducted by pooling these studies may provide new and clinically useful information. In attempts to minimize the impact of blood loss at the time of surgery, and consequently, to avoid RBC transfusion, many treatment modalities have been tried, from advanced techniques in operative procedure and anesthesia alongside with newer drugs to stimulate hematopoiesis to minimize transfusion. Although a large systematic review has shown that antifibrinolytic drugs reduce blood loss and consequently the rate of RBC transfusion [124, 125],

it would appear that these drugs, while reducing blood loss, are associated with a hypercoagulable state [126]. Similarly, thrombotic events are reported with the erythropoiesis-stimulating agents [127]. Iron plays an essential role in erythropoiesis and is a fundamental component in RBC formation [128]. Thus, use of iron is a compelling potential intervention to treat preoperative anemia. However, existing evidence is uncertain [129, 130]. In non-surgical settings, it has been shown that supplementation with IV iron usually results in higher Hb values [131]. Previously used IV iron preparations

such as iron sucrose (saccharate) and iron dextran have been associated with side effects [132] and anaphylactic reactions [133]. However, newer IV iron preparations, such as Venofer® (iron (III)-hydroxide sucrose), have shown better tolerability [134].

We propose to perform a systematic literature review and meta-analysis evaluating the efficacy and safety of IV iron administration to anemic patients undergoing major surgery for reducing transfusions and perioperative morbidity and mortality.

We hypothesize that IV iron is a safe and effective way to treat preoperative anemia. We further hypothesize that preoperative administration of IV iron will increase the Hb in anemic patients at risk for perioperative RBC transfusion and reduce perioperative allogeneic RBC transfusion, reduce major morbidity, and utilize fewer health resources.

We propose to perform a systematic literature review and meta-analysis evaluating the efficacy and safety of IV iron administration to anemic patients undergoing major surgery for reducing transfusions and perioperative morbidity and mortality.

We hypothesize that IV iron is a safe and effective way to treat preoperative anemia. We further hypothesize that preoperative administration of IV iron will increase the Hb in anemic patients at risk for perioperative RBC transfusion and reduce perioperative allogeneic RBC transfusion, reduce major morbidity, and utilize fewer health resources.

2.5.1. Strengths of our meta-analysis

- It will be a comprehensive search without restriction for language and time frame.
- It will include only experimental designs (RCTs and quasi-randomized studies).

- We will do critical appraisals of methodological quality for the RCT enabling us to determine whether the pooled findings are affected by study quality.

2.5.2. Limitations

Our meta-analysis might have the same unintentional biases as any meta-analysis, and these potential biases include:

1- Study selection process may inadvertently exclude relevant studies.

2- Standard methods used to conduct meta-analyses may introduce bias if studies are not sufficiently homogeneous.

3- Insufficient quantity or poor quality of the included studies.

2.5.3. Future research and policy implications of our meta-analysis

These will be guided by our final results. We expect that this study will provide the impetus for future large-scale RCTs in this field.

CHAPTER III (PAPER-II): ROLE OF PREOPERATIVE INTRAVENOUS IRON THERAPY TO CORRECT ANEMIA BEFORE MAJOR SURGERY: A SYSTEMATIC REVIEW AND META-ANALYSIS

3.1. ABSTRACT

3.1.1. Background

Preoperative anemia (reduced hemoglobin level) is a common and potentially serious hematological problem. Usually, the treatment consists of repeated allogeneic blood transfusion which is associated with increased incidence of postoperative morbidity and mortality. Preoperative intravenous iron monotherapy has been proposed as a simple intervention to reduce perioperative transfusion; however, studies are small, limited, and inconclusive. Accordingly, class 1A evidence-based medicine is not available yet due to the absence of high-quality randomized controlled trials and meta-analysis and systematic reviews. Consequently, a meta-analysis which pools these studies may provide new and clinically useful information.

3.1.2. Objective

To assess the efficacy and the safety of intravenous iron monotherapy administration versus placebo/oral iron (standard of care) in minimizing the requirement of allogeneic blood transfusions through increasing hemoglobin concentration perioperatively.

3.1.2.1. Evaluation method

A systematic review and meta-analysis of the randomized control trials comparing transfusion rate and/or hemoglobin level change between intravenous iron versus placebo or oral iron as a standard of care was performed.

3.1.3. Methods/Design

Databases of MEDLINE, EMBASE, EBM Reviews; Cochrane-controlled trial registry; Scopus; registries of health technology assessment and clinical trials; Web of Science; ProQuest Dissertations and Theses; and conference proceedings in transfusion, hematology, and surgery were searched from January 2012 to December 2016. To ensure that the search was comprehensive, reference lists of relevant studies were also examined.

3.1.3.1. Selection criteria

Titles and abstracts were screened for relevance (i.e., relevant, irrelevant or potentially relevant) by two reviewers (AE and SM) independently. The same two reviewers screened the full texts of those citations identified as potentially relevant. Eligible for inclusion in the systematic review were randomized or quasi-randomized clinical trials comparing the preoperative administration of intravenous iron with a control group (placebo or oral iron as a standard of care) to either reduce perioperative blood transfusions or increase the hemoglobin levels in patients undergoing major surgery. Studies were excluded if there was an abstract only, since an abstract alone does not provide sufficient information on findings to include it in a meta-analysis.

3.1.3.2. Analysis

To assess the heterogeneity of the included studies, subgroup analyses were conducted when it was feasible. Fixed and/or random effect models were used appropriately according to the existence of the studies heterogeneity. Random effects modeling was used where studies were heterogeneous and fixed effects modeling was used where heterogeneity was absent or low. RevMan statistical software was used for the meta-analytic analyses.

3.1.4. Results

The search found 3184 citations, and nine randomized controlled trials met the modified inclusion criteria. In total, 923 participants were included, 475 patients received intravenous iron, and 448 patients received placebo-control or oral iron as a standard of care. The meta-analysis found that preoperative intravenous iron supplementation significantly decreases allogeneic blood transfusion by 17%, resulting in fewer transfused participants in the intravenous iron group than in placebo or the standard care group (risk ratio (RR): 0.83, 95% confidence interval [CI]: 0.70, 0.98, p = 0.03) This reduction in transfusion was associated with increase in hemoglobin levels at pre-surgery time point after receiving IV iron (mean difference [MD] between the study groups: 6.65, 95% confidence interval [CI]: 0.83, 12.47g/L, P = 0.03). However, this increase in the hemoglobin level disappeared immediately after the surgery (MD between groups: -0.36, 95% CI: -1.92, 2.64 g/L, P = 0.75), or at hospital discharge (MD between groups: -0.19, 95% CI: -2.72, 2.35 g/L, P = 0.89). This drop is because some of the trials initiated the administration of IV iron 3-5 weeks before surgery and some studies started the IV

injection 1-2 days around the day of surgery. Such different timing in the methods of injection initiation resulted in a bi-phasic pattern in the Hb rise. The first wave was before surgery and the second wave was four weeks after surgery. Moreover, the blood loss perioperatively interrupted this greater hemoglobin concentration rise throughout the hospital stay. At follow-up > 4 weeks postoperatively, the hemoglobin level increased significantly again in favor of the intravenous iron group (MD: 6.46, 95% CI: 3.11, 9.80 g/L, P = 0.0002) indicating a new or an augmented effect of the injected IV iron later by the other trials.

In addition, intravenous iron resulted in a greater, significant and quicker correction of serum ferritin levels at post-treatment (pre-surgery), at hospital discharge, and > 4 weeks postoperatively, (MD between groups: 108.03, 95 % CI: 45.58, 170.49 ng/mL, P = 0.0007), (MD between groups: 547.77, 95 % CI: 36.61, 1058.94 ng/mL, P = 0.04), and (MD between groups: 391.00, 95 % CI: 271.44, 510.56 ng/mL, P < 0.00001), respectively. For non-serious and serious adverse effects, there were no differences between the two groups (RR: 1.17, 95% CI: 0.80, 1.71, p = 0.42) and (RR: 0.89, 95% CI: 0.40, 1.99, p = 0.77 respectively).

3.1.5. Conclusions

Intravenous iron supplementation monotherapy is a safe and efficacious intervention before surgery. It successfully lowers the perioperative transfusion rate and increases hemoglobin concentration pre-surgery and at four weeks postoperatively. However, further full-scale randomized controlled trials are required to give definitive

answers about its effectiveness, potential adverse events, and which intravenous iron preparation has better cost-effectiveness than the other to reduce blood transfusion.

Summary of findings for the main outcomes

Intravenous iron compared to placebo/standard of care for preoperative surgical patients

Patient or population: preoperative surgical patients
Setting: Major surgery
Intervention: Intravenous iron
Comparison: placebo/standard of care

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with placebo/standard of care	Risk with Intravenous iron				
Proportion of the transfused patients	42 per 100	35 per 100 (30 to 41)	RR 0.83 (0.71 to 0.98)	821 (7 RCTs)	⊕⊕⊕◯ MODERATE [a,b]	A sensitivity analysis with exclusion of one trial that designed mainly for autotransfusion showed higher risk reduction (19%) in favor of the intravenous iron group.
Haemoglobin level post-treatment pre-surgery	The mean haemoglobin level post-treatment pre-surgery ranged from 105-134	The mean haemoglobin level post-treatment pre-surgery in the intervention group was 6.65 higher (0.83 higher to 12.47 higher)	-	464 (6 RCTs)	⊕⊕◯◯ LOW [b,c,d,e]	A sensitivity analysis with exclusion of one trial (Edwards et al 2009) for which we had to estimate the standard deviation, the results were robust.
Haemoglobin level at post-operative day #1	The mean haemoglobin level at post-operative day #1 ranged from 93-112 g/L	The mean haemoglobin level at post-operative day #1 in the intervention group was 0.36 g/L higher (1.92 lower to 2.64 higher)	-	565 (4 RCTs)	⊕⊕⊕◯ MODERATE [b,f]	A sensitivity analysis with exclusion of one trial (Edwards et al 2009) for which we had to estimate the standard deviation, the results were robust.

Summary of findings for the main outcomes

Intravenous iron compared to placebo/standard of care for preoperative surgical patients

Patient or population: preoperative surgical patients
Setting: Major surgery
Intervention: Intravenous iron
Comparison: placebo/standard of care

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with placebo/standard of care	Risk with Intravenous iron				
Hemoglobin level at hospital discharge time	The mean hemoglobin level at hospital discharge time ranged from 100-123 g/L	The mean hemoglobin level at hospital discharge time in the intervention group was 0.19 g/L lower (2.72 lower to 2.35 higher)	-	697 (6 RCTs)	⊕⊕◯◯ LOW [g,h,i]	A sensitivity analysis with exclusion of one trial (Edwards et al 2009) for which we had to estimate the standard deviation, the results were robust.
Hemoglobin level as follow-up > 4 weeks post-surgery	The mean hemoglobin level as follow-up > 4 weeks post-surgery ranged from 122-127	The mean hemoglobin level as follow-up > 4 weeks post-surgery in the intervention group was 6.46 higher (3.11 higher to 9.8 higher)	-	441 (4 RCTs)	⊕⊕⊕◯ MODERATE [j,k]	A sensitivity analysis with exclusion of one trial (Johansson et al 2015) for which we had to estimate the standard deviation, the results were robust.
4.2 Serious adverse effects	30 per 100	27 per 100 (12 to 60)	RR 0.89 (0.40 to 1.99)	60 (1 RCT)	⊕⊕⊕◯ MODERATE [l,m]	Only one trial reported this outcome that is of small sample size.
Non-serious adverse effects	8 per 100	10 per 100 (7 to 14)	RR 1.17 (0.80 to 1.71)	803 (7 RCTs)		A sensitivity analysis with exclusion of one trial (Garrido-Martin et al 2012) that reported zero events showed exactly similar relative risk.

Summary of findings for the main outcomes

Intravenous iron compared to placebo/standard of care for preoperative surgical patients

Patient or population: preoperative surgical patients
Setting: Major surgery
Intervention: Intravenous iron
Comparison: placebo/standard of care

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with placebo/standard of care	Risk with Intravenous iron				

*The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).

CI: Confidence interval; RR: Risk ratio; MD: Mean difference

GRADE Working Group grades of evidence
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

Explanations

a. Five of the seven RCTs had a high risk of bias in one or two domains.
b. Publication bias could not be explored because fewer than 10 trials were included.
c. One trial excluded those participants with less than 80% compliance with treatment.
d. Although the heterogeneity was significant, this heterogeneity was explained by the dose and the timing of the intravenous iron injection.
e. Wide confidence (CI) interval and it overlapped 0.
f. One of the four RCTs had a high risk of bias in two domains and two RCTs had a high risk of bias in one domain.
g. There is an inconsistency between the results of the trials.
h. The CI is barely overlapping each other in some studies.
i. Publication bias could not be explored because fewer than 10 trials were included.
j. Two of the four RCTs had a high risk of bias in one domain.
k. Publication bias could not be explored because fewer than 10 trials were included.
l. The CI overlapped 1 and it is wide (including the 0.75 and 1.25 that makes the recommendations would vary if the lower versus upper CI were the true estimate.

m. Publication bias could not be explored because fewer than 10 trials were included.
n. Two of the six RCTs had a high risk of bias in two domains and an unclear risk of bias in one domain; a third study had a high risk of bias in one domain.
o. Some of the trials had the small sample size and fewer events in either group.
p. Publication bias could not be explored because fewer than 10 trials were included.

3.2. BACKGROUND

The World Health Organization (WHO) defines anemia as circulating hemoglobin (Hb) concentration less than 130 g/L in men and 120 g/L in women [6]. Preoperative anemia remains the most common hematological deficit affecting the patients undergoing elective major surgery. Moreover, it affects all patients regardless their age, sex socioeconomic class, and ethnic group, but elderly people and women in the childbearing period are more vulnerable [135, 136]. According to a systematic review, the prevalence of preoperative anemia ranges from 5% to 75%, varying on patient vulnerabilities and the proposed surgical procedure [60]. Preoperative anemia per se is associated with increased postoperative morbidity and mortality [76, 77, 137] by exposing patients to more allogeneic blood transfusion (ABT) [136]. In those patients, iron deficiency anemia (IDA) is one of the most common correctable causes of preoperative anemia [136], and this IDA is usually aggravated by acute blood loss perioperatively. In many cases, particularly in the postoperative period, the treatment usually is ABT to increase the oxygen carrying capacity and delivery to enhance patient's recovery aiming for expedited discharge. Preoperative anemia has also been revealed to be an independent risk element for perioperative ABT, postoperative morbidity [78] and 30-day postoperative mortality [73, 81, 138]. In a recent large study of 22,785 patients, after a propensity adjustment, transfusing as few as 1 or 2 units of allogeneic red blood cells (RBCs) was associated with increased morbidity and mortality [98] backing up a prior large systematic review of large-scale observational studies [99]. The findings from these two huge studies would indicate that approaches to reduce avoidable allogeneic RBC transfusions might be associated with improved postoperative outcomes. At the cost-effective level, in a

recent RBCs transfusion cost analysis study, the real expense for each RBC unit was reported to vary between US $522 and US $1,183 after estimating the direct and indirect costs, which include consumables, different blood testing, nursing time, patient moving, treatment costs, and staff fees resulting in increased cumulative total expenses [101].

Generally, the need for perioperative transfusion depends on many aspects. These elements include preoperative Hb level, perioperative blood loss quantity, clinical status of the patient and the institutional transfusion's trigger protocol. However, IDA usually is the most frequent category of anemia that develops commonly in patients undergoing major surgery [135] due to inadequate intake or blood loss. Therefore, optimization of erythropoiesis by iron supplementation may prevent the downward drift of Hb that occurs due to the acute perioperative blood loss and consequently minimizes the ABT requirement [139]. Oral iron supplementation has been used for decades to replenish the exhausted iron stores. However, it is not effective as a quick line therapy for patients scheduled for surgery due to its poor absorption and high incidence of gastrointestinal side effects. In contrast, intravenous (IV) iron supplementation allows for a large quantity of iron to be administered over a few doses and has excellent availability for erythropoiesis [140]. In addition, positron emission tomography shows fast uptake by bone marrow from the circulating blood [141]. Thus, using IV iron to correct perioperative anemia could potentially result in a faster and more efficient bloodless therapy than oral iron in replenishing depleted iron stores and enhancing hemopoiesis. The efficacy of IV iron to increase the Hb concentration significantly was shown in non-surgical settings in a recent trial [142], a review of recently published studies [143], and a meta-analysis [144].

Intravenous iron therapy for preoperative anemia has been tested in clinical trials. However, so far, the evidence to back up its safety and efficacy is unclear. Due to the paucity of the randomized controlled studies (RCTs), most of which are of small sample size and have negative outcomes, which may be a result of being underpowered, there is insufficient evidence to support the use of IV iron to decrease RBCs transfusion. A meta-analytic approach would aid in addressing the limitations of trial size, which would increase the power to observe statistically significant differences where these exist and may provide new and clinically useful evidence.

In this meta-analysis, randomized and quasi-randomized trials were assessed. Intravenous iron was compared with different preparation versus placebo or oral iron supplementation as a standard of care to increase the Hb, to reduce transfusions, and to improve outcome.

3.3. OBJECTIVES

To perform a systematic review and evidence synthesis, through meta-analytic techniques of all randomized and quasi-randomized studies investigating (a) the ability of parenteral iron administration to minimize ABT requirement by improving preoperative Hb concentrations, and (b) the safety of parenteral iron in terms of mortality, morbidity, and adverse events (AEs) compared to placebo/oral iron as standard of care.

3.4. PATIENTS AND METHODS

3.4.1. Protocol and Registration

This systematic review and meta-analysis protocol has been published [145] and registered online in advance with the International Prospective Register of Systematic Reviews (PROSPERO), systematic review registration number: PROSPERO CRD42015016771) on 16 February 2015. The current study was conducted and reported following the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) statement [145].

Eligibility Criteria

To be eligible, a study had to be a randomized controlled clinical trial in which the intervention drug was IV iron as monotherapy, initiated preoperatively, which was compared to either placebo or oral iron as a standard of care. To be comprehensive, there were no restrictions applied regarding participants' sex, IV iron preparations, doses, treatment course or duration of therapy. To capture the trials, I did not apply publication date/status or language restrictions. I excluded any study that was available as an abstract only, since an abstract alone does not provide sufficient information on findings to include it in a meta-analysis.

Search Strategy

With the help of a health sciences librarian, the following databases were searched: MEDLINE, EMBASE; EBM Reviews; the Cochrane-controlled trial registry in the Cochrane Library; Scopus; registries of health technology assessment and clinical trials; and Web of Science. Also searched were the ProQuest Dissertations and Theses database; the ClinicalTrials.gov website (National Institute of Health) for completed but unpublished studies; and recent international conference proceedings over the last five

years from 2012 to 2016. These meetings were The American Society of Hematology (ASH) Meeting, The American Association of Blood Banks (AABB) Conference, The American Association of Thoracic Surgeons (AATS) Congress, The Society of Thoracic Surgeons (STS) Meeting, and The European Society of Cardiovascular Surgery (ESCVS) Conference. The search was started from the earliest retrievable date of each database to December 2016, supplemented by a manual search of reference lists of all retrieved trials. Reference lists of prior reviews of related areas were searched for relevant trials. Moreover, a comprehensive search on Google engine to identify studies published in a journal that was not indexed in the databases. The search strategy is presented in Appendix 1.

3.4.2. Study Screening

All study screening was conducted by authors AE and SM. Initially, these two authors reviewed the titles, abstracts, and reference lists of all included publications to retrieve potentially relevant studies. The full text of retrieved studies was subjected to a second phase of screening for eligibility as defined by the inclusion/exclusion criteria (updated and published on the PROSPERO website on April 27, 2017) and study design, for methodological quality. In cases of disagreements about eligibility of a study, consensus was accomplished through discussion.

3.4.3. Modified Article Selection Criteria

Based on the inclusion/exclusion criteria in the published protocol, I found only one eligible trial to be included in the meta-analysis. Consequently, I had to modify the meta-analysis inclusion/exclusion criteria to recruit more studies. Accordingly, all trials studied

non-anemic participants were included and all studies in which IV injection was initiated pre-surgery (even the treatment completion happened post-surgery) were involved even the iron treatment completed post-surgery.

Inclusion criteria

Eligibility criteria of studies were as follows:

1- Designs included were randomized and quasi-randomized studies in all different phases of clinical research.
2- Study compared any IV iron that was initiated preoperatively to placebo or standard of care (oral iron).
3- Study reported findings specific to adult humans.
4- Study included patients undergoing any elective major surgery including, but not limited to, cardiac, thoracic, orthopedic, gastrointestinal, brain, urologic, or gynecologic operations.
5- Study reported at least one of the two following outcomes: absolute or relative change in preoperative Hb concentration and/or the proportion of patients received perioperative ATB.

Exclusion criteria

Any one of these criteria resulted in a study being excluded:

1- Observational (non-experimental) studies, reviews, opinion papers, letters to the editor, and studies with no reported methodology.
2- Studies with no adult-specific findings.
3- Studies used oral iron only.

4- Studies used IV iron plus erythropoietin (EPO).

5- Studies of minimally invasive robotic and laparoscopic surgery.

3.4.4. Data Extraction

The same two authors (AE and SM) reviewed the relevant studies and extracted the relevant data using a structured form. Data extracted by the two reviewers included primary efficacy outcomes, safety outcomes (AEs, mortality, and morbidity), participant's population, references, and funding. Where studies included more than two arms within a trial that compared IV iron with placebo and oral iron; only the IV iron and placebo arms were included, so each patient was used only once. The primary efficacy outcomes were the proportion of study participants who received an ABT, reflecting the association between the pre-surgery injection of IV iron and the need for RBCs transfusion, and the change of the Hb concentration between those who received and who did not receive IV iron, reflecting the hematopoietic response. Secondary outcomes included mortality, and number of units of RBCs or any blood products transfused perioperatively, transfusion-related acute lung injury, AEs, postoperative infections, cardiopulmonary complications (like any myocardial event or pneumonia), intensive care unit (ICU) admission time or readmission, the length of hospital stay (LOS), and quality of life if it were reported. Data are presented in evidence tables and meta-analytic forest plots.

3.4.5. Assessment of the Risk of Bias

To evaluate the sources of bias in the included RCTs, the Cochrane Collaboration's tool for evaluating the risk of bias was used. This tool is used to assess the following domains of bias: random sequence generation, allocation concealment

(selection bias), blinding of trial's participants and trial's investigators (performance bias), blinding of outcome assessment (detection bias), incompleteness of outcome data (attrition bias), selective outcome reporting (reporting bias), and other sources of bias as marked baseline discrepancies in predictive factors. Each domain for each trial had a ranking of "low," "unclear," or "high" risk of bias according to the Cochrane Collaboration's approach [146]. AE and SM independently appraised each study, with discrepancies between appraisers resolved through discussion.

3.4.6. Data Synthesis and Analysis:

As above, one of the primary outcomes of the study was the proportion of study participants who received an ABT, which were analyzed as risk ratios (RR) with their 95% confidence intervals (CIs) reflecting the association between the pre-surgery injection of IV iron and the need for RBCs transfusion. The second primary outcome was the hematopoietic response, which was analyzed as the mean difference (MD) in the change of the Hb concentration with its statistical significance between those who received and who did not receive IV iron. Safety outcomes, like mortality, infection, and the percentage of study patients reporting severe or mild treatment-related AEs were also included.

Dichotomous variables were presented as percentage and the continuous variables described as the mean ± standard deviation (SD). For continuous outcome measures like Hb and ferritin levels, the MD and the associated 95% CIs were calculated for all trials by inverse variance method. Dichotomous outcomes like the rate of ABTs, the AEs, the morbidity, the mortality, and the infection, the pooled relative risk (RR) with 95% CIs was calculated by Mantel- Haenszel method.

Because I have fewer than ten studies, I was not able to accomplish a meta-regression to evaluate the impact of potential confounding variables on study effect estimates, to relate the findings of the studies to the participants' characteristics within the trials, and to identify the heterogeneity sources between trials even if the initial overall test for heterogeneity was non-significant since a non-significant test result does not necessarily exclude the existence of heterogeneity [147]. Some of the included studies did not report the SD. To solve the problem of missing value, trial authors were contacted in an effort to get the primary data to compute it. Thus, where the SD was not reported in the study, it was estimated from 95% CIs, z-statistics, P-values, or imputed using the largest reported SD from the other trials [148]. Use of the fixed and/or the random effects models was planned, depending on how much statistical heterogeneity existed between the studies. Generally, the included studies in a meta-analysis are likely to be conducted by researchers operating independently; this would be unlikely that all those trials' findings are similar statistically. Therefore, it would not be plausible to assume a common effect size [149]. Typically, the fixed effects model estimates a single effect that is assumed to be common to every trial in the meta-analysis, while the random effects model estimates the mean of a distribution of effects considering the statistical heterogeneity existing between the studies. Consequently, the trial weights in the meta-analysis are more balanced under the random-effects model than under the fixed effect model. Moreover, the CIs for the effect size are wider under the random-effects model than under the fixed effect model [149].

The Cochran Q test was used to calculate the statistical heterogeneity among studies. An I^2 value >40% suggests important statistical heterogeneity and a random

effect model (DerSimonian and Laird technique)[150] is appropriate. In the case of absent or low heterogeneity (I^2 value <40%) [151], the fixed effect model (Mantel-Haenszel technique)[152] is appropriate, with a random-effects model as a sensitivity analysis. The Z-test was used to test the overall effect. I did a sensitivity analysis on the proportion of ABT, the Hb level change as primary efficacy outcomes, and the proportion AEs as a safety outcome by excluding trials with a high risk of bias for one or more key domains according to the Cochrane Collaboration's tool for evaluating the risk of bias [151].

In the analyses, to avoid moving the pooled estimate of IV iron treatment effect closer to nil [153], initially, all trials reporting zero-event data for both trial arms were excluded from the analysis [154]. Then, the analysis was repeated including the studies with zero events to say if there was a change in the analysis result and to offer more generalizability in the clinical practice for the treatment effect estimate by including all the available data from the entire studies [153]. Across the meta-analysis, the statistical significance was set as p-value smaller than 0.05.

Subgroup analysis and exploration of heterogeneity

To assess the heterogeneity of the included studies, subgroup analyses were planned when feasible by having at least two studies in at least two subgroups for the proportion of the transfused patients as a primary outcome. The following subgroup analyses were planned if possible: 1) cardiac versus non-cardiac trials; 2) different IV iron preparations; 3) preoperative Hb concentration value; trials with a mean Hb equal to or greater than 100 g/dL; and 4) age; studies with a mean age over the age of 65 years.

The approach of “leave-one-out’’ sensitivity analysis was implemented to assess the stability of the meta-analysis outcomes [154]. In this approach, I conducted a set of meta-analyses on each subset of the trials, leaving out one study at a time to see how that individual trial influenced the overall estimate of the rest of the trials.

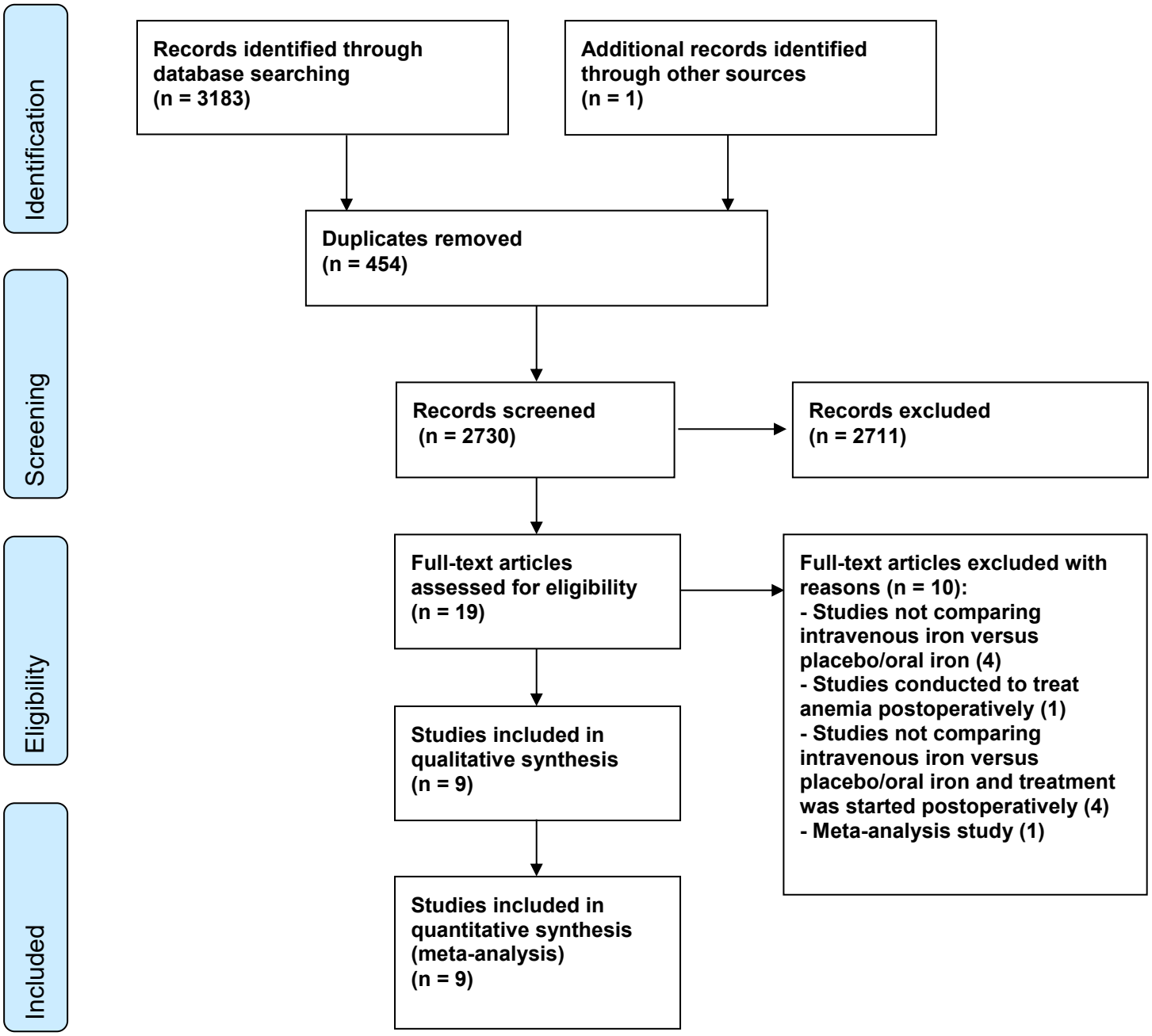
RevMan 5.3 software: The Nordic Cochrane Centre, The Cochrane Collaboration; 2014 [121] was used to perform the analysis.

3.5. RESULTS

The initial electronic search yielded 3184 citations. After reviewing the titles, and abstracts, ten studies were retrieved for more thorough screening, and one trial, which was published only as an abstract was excluded (Figure 1). That study’s authors were contacted, but they declined to provide us their data. Consequently, a total of nine RCTs met the inclusion criteria. In these nine studies, there was a total of 923 participants (475 in the IV iron group and 448 in control group). All patients were scheduled to have elective major surgery; two studies involved orthopedic surgery, two involved cardiac surgery, two involved gynecological surgery, one involved major abdominal surgery, one involved colorectal surgery, and one involved orthopedic/cardiovascular surgery. The mean age of participants in seven of the trials [108, 129, 155-159] ranged from 42 ± 7.4 to 84.6 ± 6.2 years in the IV iron group and from 42 ± 8 to 82 ± 6 in the control group. One trial [130] reported median ages only, which were 67 years old and 70 years old in the IV iron and control group respectively. The remaining trial [160] reported that 82% and 80% of

participants’ ages ranged between 30 to 50 years for the IV iron and control group correspondingly. The trials' baseline Hb level varied from 71.8 ± 11.8 to 142.5 ± 22.3 g/L in the patients obtaining IV iron group, and from 71.8 ± 10.2 to 142 ± 13 g/L in the patients who did not have IV iron therapy.

Figure 1: Study flow chart.



The included trials were heterogeneous regarding the treatment dosage. Moreover, they used different IV iron preparations. Among the included studies, IV iron sucrose was the most common drug given, and it was used in six trials [108, 129, 130, 158-160], followed by ferric carboxymaltose in two trials [155, 156], and iron isomaltoside in one trial [157]. In those participants receiving IV iron, 302 received iron sucrose, 143 received ferric carboxymaltose and 30 received iron isomaltoside. In the IV iron therapy arms, the mean parenteral iron quantity received ranged between 300 and at least 1000 mg. All trials completed the full target dose of IV iron administration preoperatively except for two trials [108, 129] where the IV iron injection was initiated at the pre-surgery time, and the rest of the dose was completed after surgery. The follow-up went beyond hospital discharge in four trials, where a follow-up was achieved at a four-week period post-surgery in two trials [156, 157], a month post-hospital discharge in one trial [129], and a two-month post-hospital discharge in one trial [155]**.** The publication dates of the included trials ranged between 1999 and 2016. The different characteristics of the included trials and the dose regimen of IV iron administration for each trial are summarized in the nine tables of Appendix 6.

Table 2: Characteristics of included studies

Study	*Country*	*Surgery type*	*Mean age (SD): Intravenous iron/control or oral iron*	*Patients #: Intravenous iron/control or oral iron*	*Anemic Patients were recruited*	*Comparator*	*Intravenous iron dosage regimen*	*Last follow-up time*
Bernabeu-Wittel et al., 2016	Spain	Hip fracture surgery	84.6 ± 6.2/ 82.3 ± 6.9	103/100	Yes	Placebo	1000 mg of IV Ferric carboxymaltose (two 500 mg vials diluted in a bottle of 250 mL of saline.	60 days post-discharge
Edwards et al. 2009	UK	Colorectal cancer resection	67/70 (median)	34/26	Some patients were anemic	Placebo	300 mg iron sucrose in 2 infusions separated at least 24 h apart, 14 days pre-surgery.	Hospital discharge
Froessler et al. 2016	Australia	Major Abdominal Surgery	64 ± 15 / 68 ±15	40/32	Yes	Usual care	Ferric carboxymaltose, 15 mg/kg with maximum dose of 1000 mg. Post-surgery, within two days of surgery, participants received 0.5 mg of ferric carboxymaltose per recorded 1 mL of blood loss, if blood loss was > 100 ml.	Four weeks post-surgery.
Garrido-Martín et al. 2012	Spain	On-pump cardiac surgery	65 ± 11/ 65 ± 12	54/52	No	Placebo	iron sucrose 100 mg /24 h during pre- and postoperative hospitalization.	One-month post-discharge
Kim et al. 2009	South Korea	Gynecological surgery for menorrhagia	42.0 ± 7.4/ 42.3 ± 8.0	30/26	Yes	Oral iron	200 mg iron sucrose three times a week starting three weeks prior surgery until target hemoglobin of 10 g/dL was achieved.	Hospital discharge
Johansson et al. 2015	Denmark	30/26	65 ± 8/ 65 ± 11	26/25	No	Placebo	A single-dose infusion of 1000 mg with a maximum single dose of 20 mg/kg.	Four weeks after surgery
Serrano-Trenas et al. 2011	Spain	Hip fracture surgery in elderly patients	83.46 ± 7/ 82 ± 6	99/97	Some patients were anemic	standard protocolized treatment	Iron sucrose 200 mg at 48-hour intervals for 3 doses, starting on the day of admission; the first dose was given pre-surgery. The following doses were administered before or after surgery, depending on the time of surgery.	Seven days posy-surgery
Shah et al. 2016	India	Gynecological surgery for menorrhagia	Most of ages are between 40 and 49 years	55/55	Yes	Oral iron	100 mg iron sucrose in 100 ml by slow IV infusion. The dose was repeated on alternate day basis until target hemoglobin of 10 g/dL was achieved.	Hospital discharge
Weisbach et al. 1999	Germany	Orthopedic or cardio-vascular surgery	64.4 ± 14.7/64.1 ± 9.5	30/30	No	Usual care	200 mg of iron sucrose, given after each donation and at the enrollment before the first donation	Hospital discharge

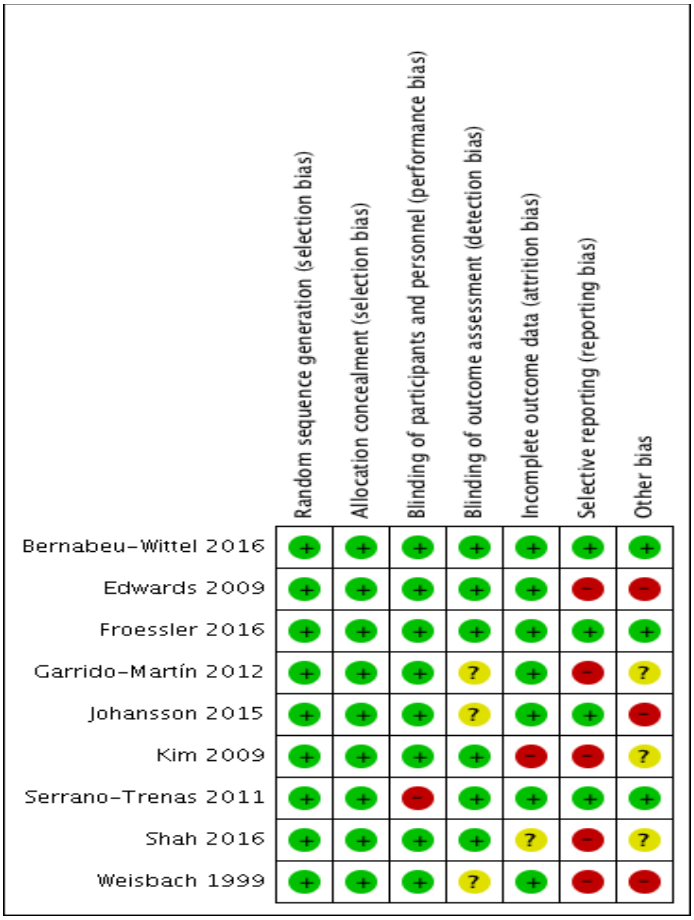
3.5.1. Risk of Bias Assessment

Two studies [155, 156] of the nine trials were judged as having a low risk of bias across the entire set of domains, while seven trials [108, 129, 130, 157-160] were assessed to have a low risk, medium risk or high risk of bias in different domains. Selective reporting bias and “other” biases mainly drove this. Details of the risk of bias judgment for each study are shown in Figure 2, and item-specific judgments for studies are presented in Figure 3. In all included trials, there was proper random sequence generation and allocation concealment, reducing the selection bias in the meta-analysis. All studies reported details on the method used for randomization. For blinding of the participants and personnel, one trial [108] had probable performance bias due to unblinding of participants and staffs. Two trials [158, 160] did not blind the participants where one arm was receiving oral iron. However, when comparing IV iron to oral iron, blinding would be difficult due to the effect of oral iron on stool color. However, lack of blinding in this kind of study is less likely to generate bias when calculating measurable outcomes like Hb, blood transfusion, mortality and ferritin levels. With respect to the blinding of outcome assessment, six trials [108, 130, 155, 156, 158, 160] had a low risk of detection bias, and three trials [129, 157, 159] had a medium (unclear) risk of detection bias. With respect to incomplete outcomes data, seven of the trials [108, 129, 130, 155-157, 159] had a low risk of attrition bias, one trial [160] had a medium (unclear) risk of bias, and one study [158] had high risk of bias, which was driven by exclusion of the participants data whose compliance was less than 80% in the final analysis. Concerning selective outcome reporting (reporting bias), five trials [129, 130, 158-160] had a high risk of bias driven by non-reporting of necessary outcome data (mortality/ABT or both), and

four trials [108, 155-157] had a low risk of bias for non-reporting mortality data. Two of these four trials [158, 160] did not report ABT necessity data, which is important and relevant information for the meta-analysis. For other sources of bias, three trials [108, 155, 156] had a low risk of bias, three trials [129, 158, 160] had a medium (unclear) risk of bias, and three studies [130, 157, 159] showed a high risk of biases.

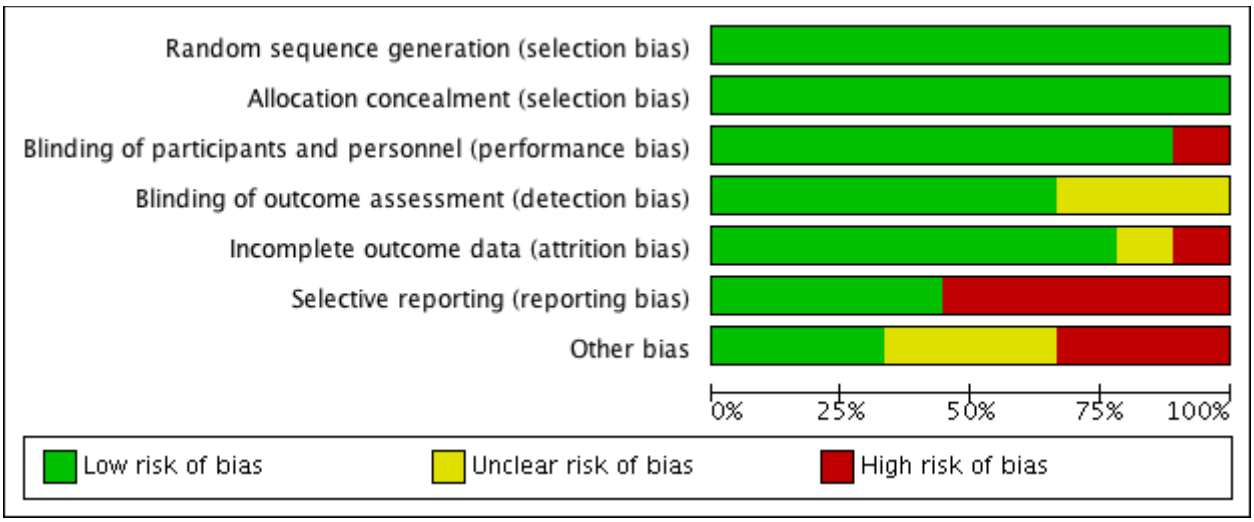
The primary outcomes in this meta-analysis were measured as the proportion of ABT and the change of Hb level perioperatively. For the proportion of ABT, as an efficacy outcome, seven [108, 129, 130, 155-157, 159] of nine trials contributed to the pooled estimates analysis of the proportion of transfused patients. The other two trials [158, 160] did not report transfusion data; instead, those two trials investigated whether preoperative IV iron injection augmented erythropoiesis in anemic women undergoing gynecological surgery. Moreover, these two trials [158, 160] studied younger patients compared to the other seven trials' participants. For the Hb concentration change, all nine included trials [108, 129, 130, 155-160] contributed to the Hb change analysis at different time points but none of them provided data for all the time points and during the follow-up visits. The time points in this study were: at baseline, at pre-surgery, at the first postoperative day, at hospital discharge, and greater than four weeks postoperatively as a follow-up.

Figure 2: Risk of bias summary shows the authors' judgment about each risk of bias item for each included study.



The symbol '+' represents a low risk of bias, the symbol '-' represents a high risk of bias, and the symbol '?' represents an unclear risk of bias.

Figure 3: Risk of bias graph shows the authors' judgment about each risk of bias item presented as percentages across all included studies.



3.5.2. Exposure for allogeneic blood transfusion

Overall, IV iron injection showed significantly higher efficacy, achieving a reduction of 17% in the proportion of patients requiring ABT. This pooled effect estimate was statistically significant (risk ratio (RR) between the IV iron group and the control group: 0.83, 95% CI: 0.70, 0.98, p = 0.03) as presented in Figure 4. Under the random-effects model, the reduction was significant as well while it decreased to 16% (RR: 0.84, 95% CI: 0.71, 1.00, p = 0.04) as presented in Figure 5. In both models, there was no heterogeneity in ABT observed based on the Cochran Q statistic (p = 0.48) and the corresponding I^2 statistic was 0%, interestingly, there are some variations in the result of each model. These variations could be due to having few numbers of the included trials (7 studies) contributing to the analysis. Therefore, these statistical analyses results may be prone to type II error indicating a shortage of power to identify trials' heterogeneity. However, the trials' heterogeneity was explored using sensitivity and subgroup analyses. Because there was a study [159] that designed mainly to evaluate the capability of IV iron

administration to improve autologous blood donation pre-surgery. Moreover, most of this study's participants donated at least three times as autologous blood transfusion preoperatively. In a sensitivity analysis excluding this study, the reduction of ABT increased to 19% under the fixed effects model (RR: 0.81, 95% CI: 0.68, 0.96, p = 0.01) as presented in Figure 6.

In this meta-analysis, given the existence of many trials of different kinds of major surgeries that used different IV iron preparations, subgroup analyses were conducted comparing the cardiac versus the non-cardiac studies and iron sucrose versus the ferric carboxymaltose IV iron preparation. In the subgroup analyses, there was no a significant difference between non-cardiac surgery trials [108, 130, 155, 156] and cardiac surgery trials, under the random effects (RR: 0.80, 95% CI: 0.60, 1.07, p = 0.13) as revealed in Figure 7. For the different IV iron preparations, only under the fixed effects model, there was statistically significant difference in the subgroups analysis between the studies [108, 129, 130, 159] using iron sucrose and those studies [155, 156] using ferric carboxymaltose where fewer patients received transfusion in the iron sucrose subgroup (RR: 0.84, 95% CI: 0.70, 0.99, p = 0.04) as presented in Figure 8. Intrestingly, under the random effects where the I^2 was only 7%, there was not a significant difference between the subgroups (RR: 0.84, 95% CI: 0.70, 1.01, p = 0.07) as displayed in Figure 9.

Figure 4: Forest plot comparison shows the pooled comparison effect of intravenous iron therapy versus placebo/standard of care groups on the proportion of the transfused patients (fixed effects model).

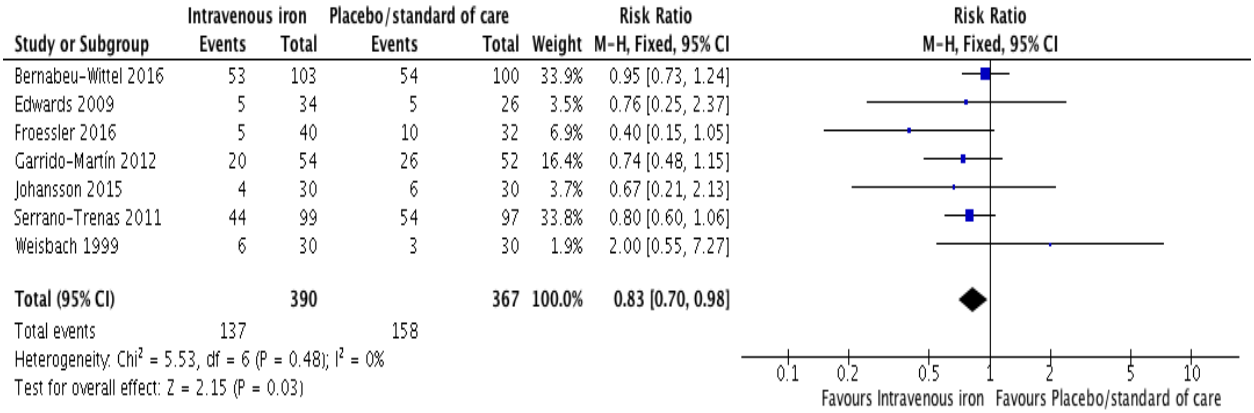


Figure 5: Forest plot comparison shows the pooled comparison effect of intravenous iron therapy versus placebo/standard of care groups on the proportion of the transfused patients (random effects model).

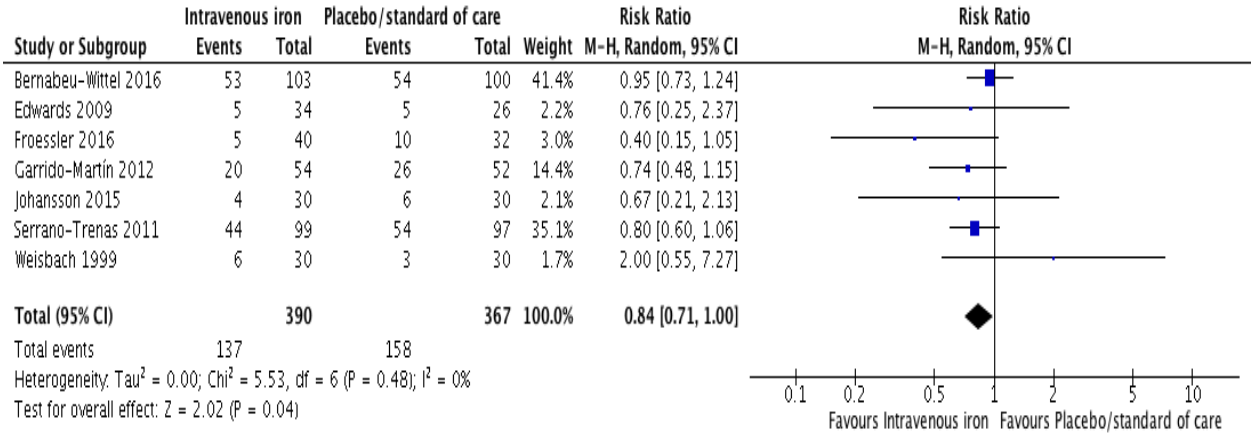


Figure 6: Forest plot comparison shows the pooled comparison effect of intravenous iron therapy versus placebo/standard of care groups on the proportion of the transfused patients after exclusion of Weisbach trial as a sensitivity analysis (fixed effects model).

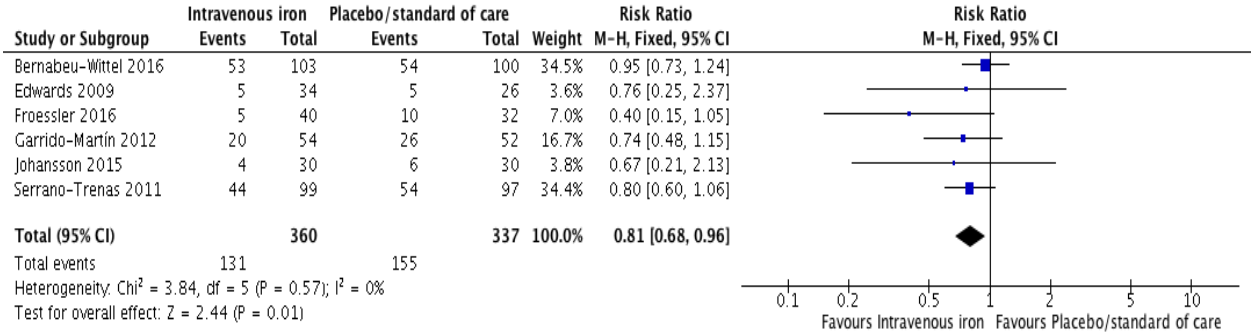


Figure 7: Forest plot comparison shows the pooled comparison effect of intravenous iron therapy versus placebo/standard of care groups on the proportion of the transfused patients with the different surgeries as a subgroup analysis (random effects model).

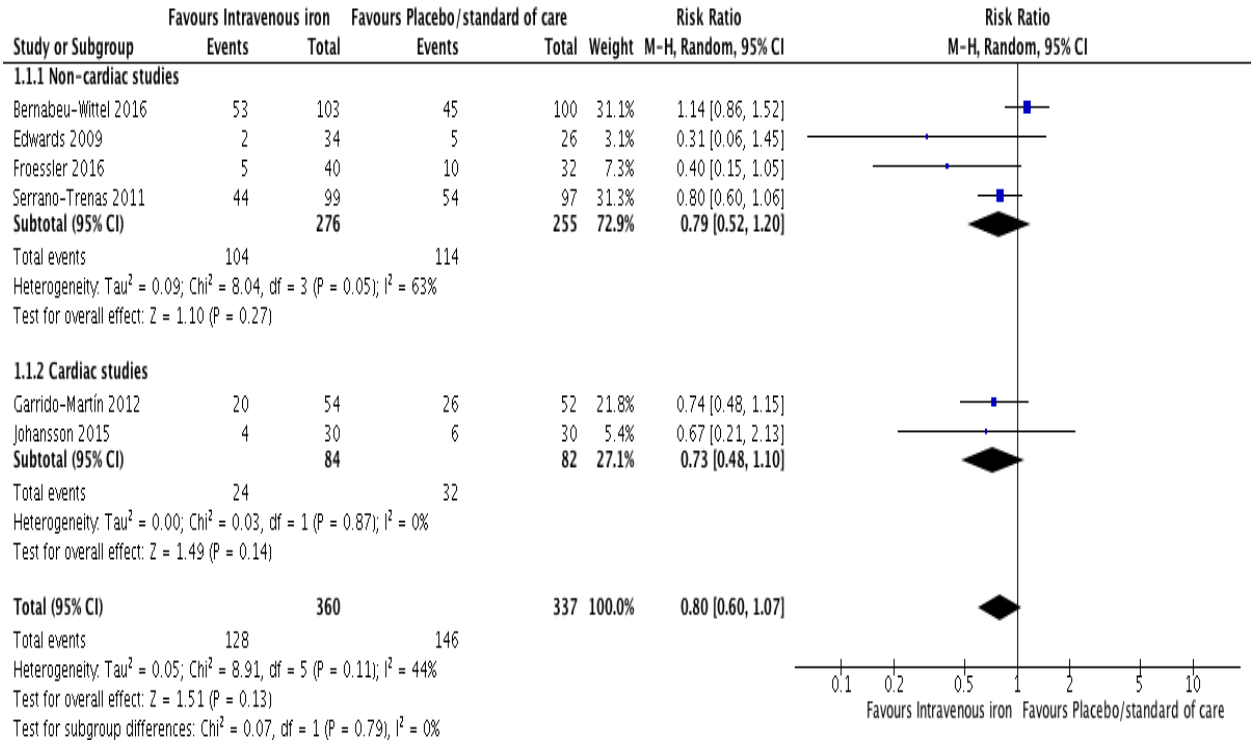


Figure 8: Forest plot comparison shows the pooled comparison effect of intravenous iron therapy versus placebo/standard of care groups on the proportion of the transfused patients as a subgroup analysis for different intravenous iron preparations (fixed effects model).

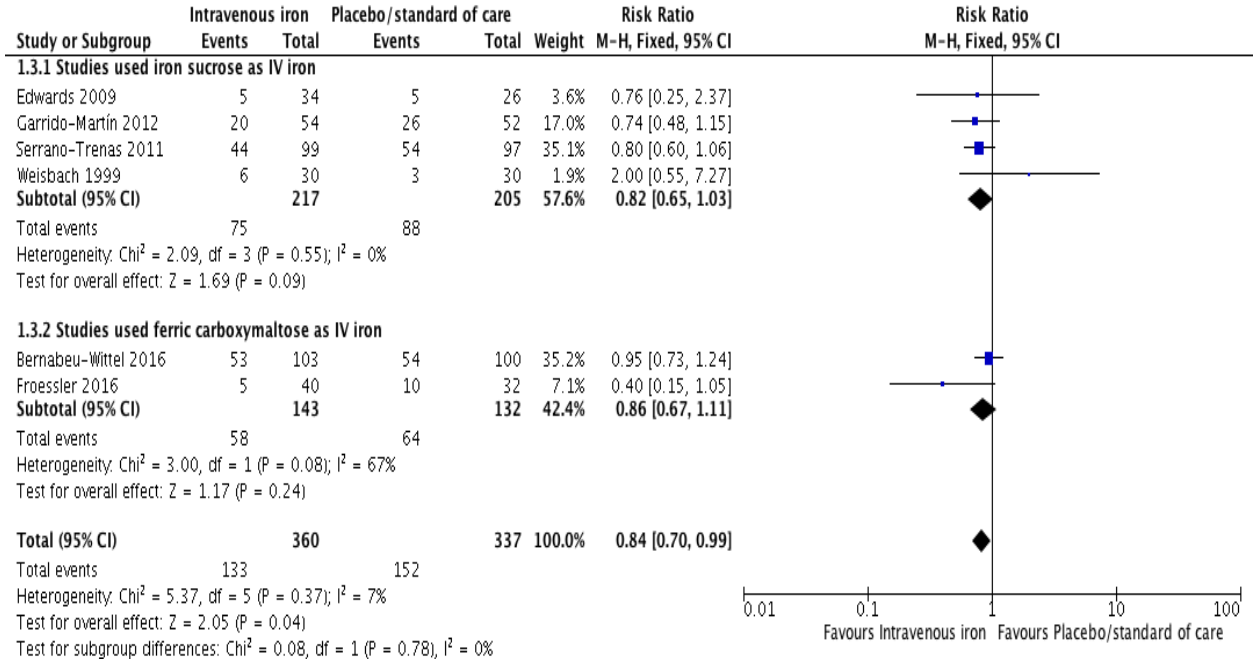
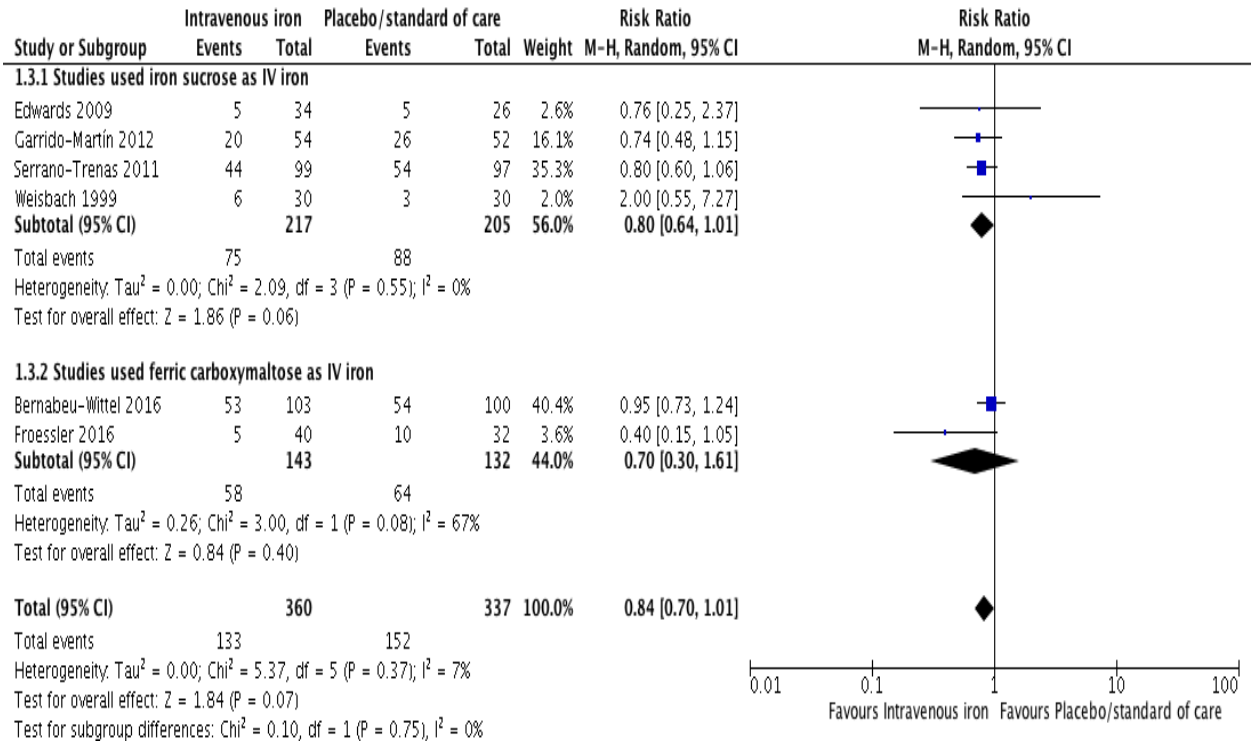


Figure 9: Forest plot comparison shows the pooled comparison effect of intravenous iron therapy versus placebo/standard of care groups on the proportion of the transfused patients as a subgroup analysis for different intravenous iron preparations (random effects model).



3.5.3. Hemoglobin concentration change

All the included trials [108, 129, 130, 155-160] provided data for the Hb levels changes in those receiving IV iron monotherapy. At the baseline level, since the pooled means of trials' participants were equivalent (116.14 g/L in the IV iron group and 116.07 g/L in the control group), accordingly, the pooled estimate analysis presenting comparability between the two meta-analysis groups (MD: 0.15, 95% CI: -1.31, 1.60 g/L, p = 0.84) where all the trials contributed to the calculation of the MD as revealed in Figure 10 under the random effects model. After completion of the preoperative IV iron administration, a significant Hb level increase in the IV iron group was achieved before going to surgery compared to the placebo or oral iron group under the random effects model (MD between groups: 6.65, 95% CI: 0.83, 12.47g/L, p = 0.03) based on existing

heterogeneity (Cochran Q statistic of $p < 0.0001$ and the corresponding I^2 statistic of 82%) as shown in Figure 11. On following this rise in difference at the pre-surgery time, the difference dropped rapidly throughout the hospital stay and there were no significant differences noted at the first postoperative day between the two meta-analysis groups (MD between groups: -0.36, 95% CI: -1.92, 2.64 g/L, p = 0.75) as shown in Figure 12, or at hospital discharge (MD between groups: -0.19, 95% CI: -2.72, 2.35 g/L, p = 0.89) as shown in Figure 13. After the hospital discharge, for follow-up > 4 weeks postoperatively, only four trials [129, 155-157] reported data at this time point. The pooled effect of three of them showed a significant increase in the Hb difference in favor of the IV iron group, where a more significant effect estimate was seen (MD between groups: 6.46, 95% CI: 3.11, 9.80 g/L, p = 0.0002) as displayed in Figure 14. In addition, one study [157] of the four trials that contributed to this analysis, at 5 days postoperatively, it showed equivalent proportion of non-anemic patient (p = 0.49) but at 4 weeks postoperatively, the study results showed more participants with normal Hb in the IV iron arm: i.e., 10 (38.5%) patients with normal Hb in the IV iron arm compared to 2 (8.0%) patients with normal Hb patients in the placebo arm, p = 0.02. In that study, although the mean Hb level was reduced from baseline to the fourth-week post-surgery in both trial arms, IV iron administration was relatively protecting, and greater proportion of participant had a Hb value > 12.5 g/dl in the iron than the placebo group (53.8% versus 24.0 %; p = 0.03).

Figure 10: Forest plot comparison shows the pooled comparison of baseline value of hemoglobin level (g/L) between intravenous iron therapy versus placebo/standard of care groups (random effects model).

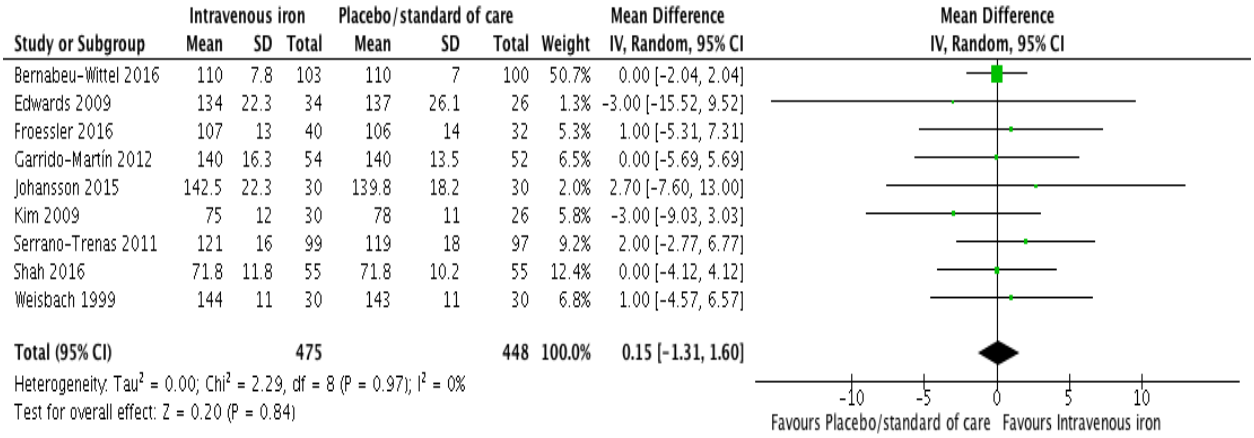


Figure 11: Forest plot comparison shows the pooled comparison effect of intravenous iron therapy versus placebo/standard of care groups on the change of hemoglobin level (g/L) at the post-treatment (pre-surgery) time (random effects model).

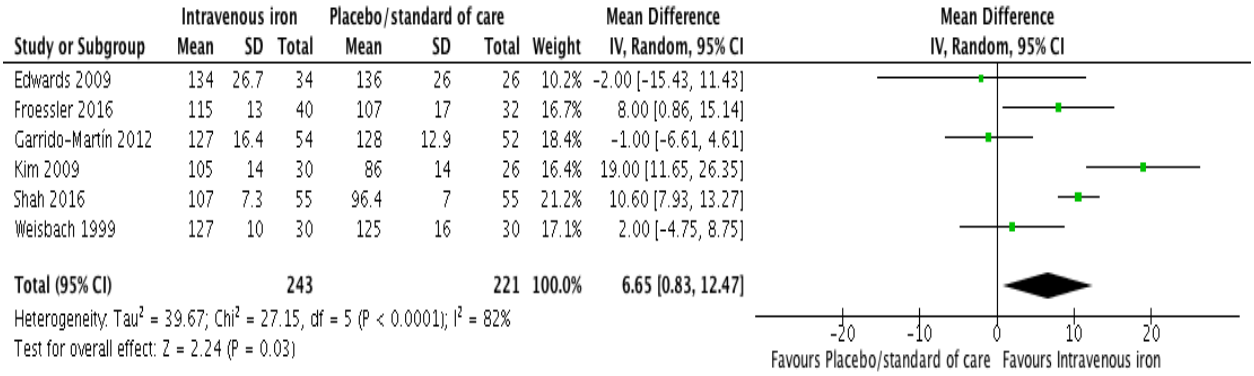


Figure 12: Forest plot comparison shows the pooled comparison effect of intravenous iron therapy versus placebo/standard of care groups on the change of hemoglobin level (g/L) at postoperative day # 1 (random effects model).

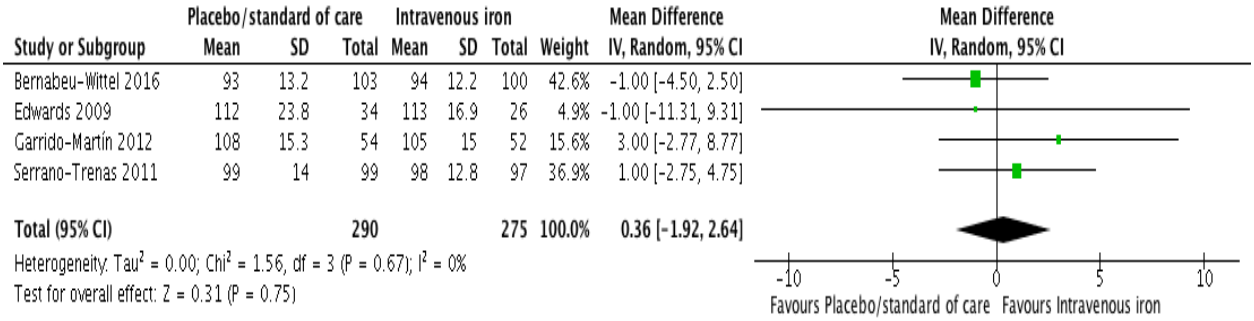


Figure 13: Forest plot comparison shows the pooled comparison effect of intravenous iron therapy versus placebo/standard of care groups on the change of hemoglobin level (g/L) at the hospital discharge (random effects model).

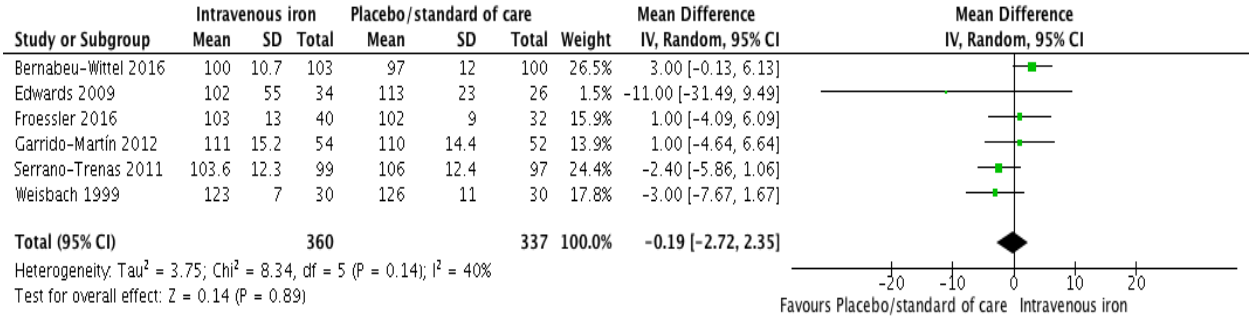
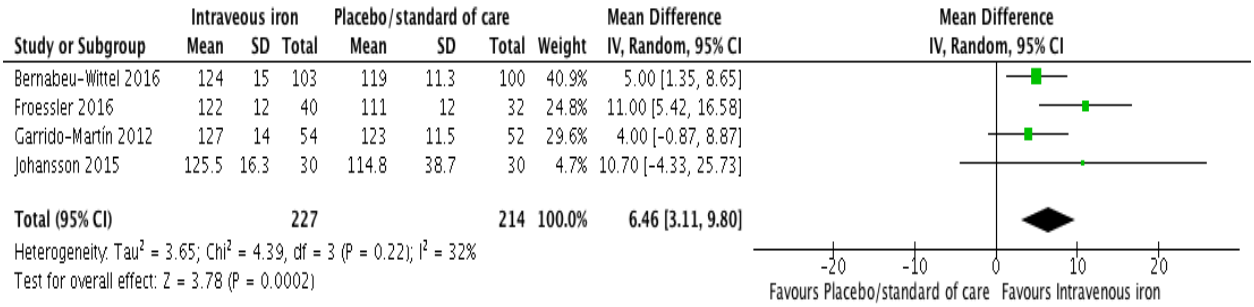


Figure 14: Forest plot comparison shows the pooled comparison effect of intravenous iron therapy versus placebo/standard of care groups on the change of hemoglobin level (g/L) as follow-up > 4 weeks postoperatively (random effects model).



3.5.4. Hematocrit value %

For the second hematopoietic parameters after Hb, only two trials [108, 130] provided statistics for the hematocrit (Hct) percent. The randomization did not work to equalize baseline characteristics, and the hematocrit value was higher significantly in the IV iron group (MD between groups: 0.69, 95% CI: 0.10, 1.28%, p = 0.02) as indicated in Figure 15. Nevertheless, Hct values were equivalent across groups on the first day after surgery (MD between groups: 0.31, 95% CI: -0.28, 0.89%, p = 0.31) and on the hospital discharge (MD between groups: 0.40, 95% CI: -0.38, 1.19%, p = 0.31) as shown in Figure 16 and Figure 17.

Figure 15: Forest plot comparison shows the pooled comparison of baseline value of the hematocrit percentage (%) between intravenous iron therapy versus placebo/standard of care groups (random effects model).

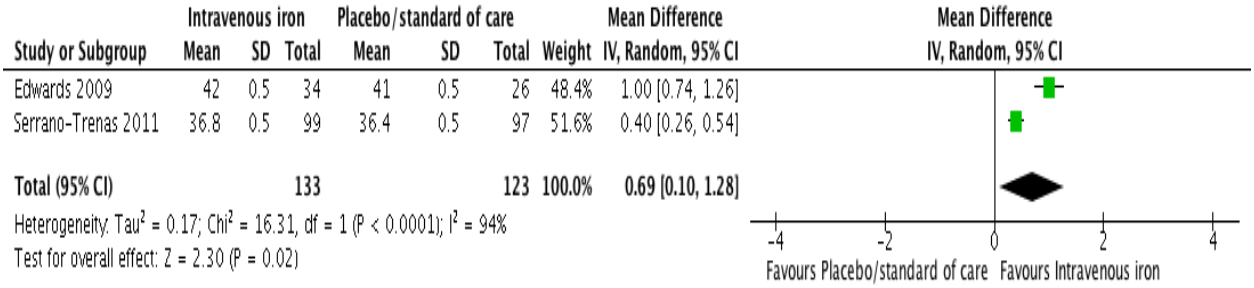


Figure 16: Forest plot comparison shows the pooled comparison effect of intravenous iron therapy versus placebo/standard of care groups on the hematocrit value (%) at postoperative day # 1 (random effects model).

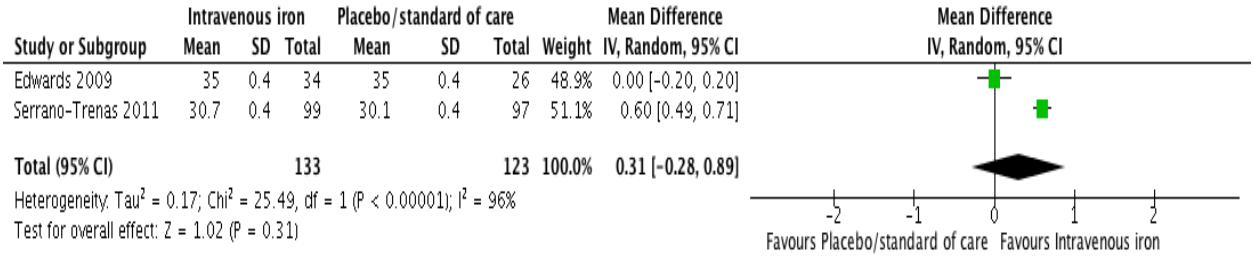
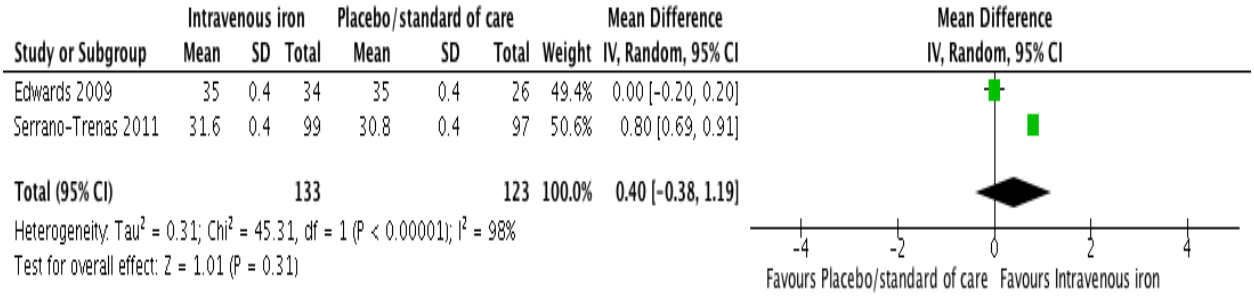


Figure 17: Forest plot comparison shows the pooled comparison effect of intravenous iron therapy versus placebo/standard of care groups on the hematocrit value (%) at the hospital discharge (random effect model).



3.5.5. Ferritin levels

Seven trials [108, 129, 130, 155, 157-159] of nine RCTs contributed to the analysis of mean ferritin level at baseline. While the pooled means of trials' participants were 177.83 ng/mL in the IV iron and 146.03 ng/mL in the control group, statistically, they had similar pooled comparison across groups (MD: 10.36, 95% CI: -23.65, 44.36 ng/mL,

p = 0.55) as exhibited in Figure 18. With the administration of the IV iron, marked improvements in iron stores replenishment were observed. Consequently, serum ferritin levels increased significantly in favor of the IV iron group at post-treatment (pre-surgery), at hospital discharge, and > 4 weeks postoperatively, (MD between groups: 108.03, 95 % CI: 45.58, 170.49 ng/mL, p = 0.0007), (MD between groups: 547.77, 95 % CI: 36.61, 1058.94 ng/mL, p = 0.04), and (MD between groups: 391.00, 95 % CI: 271.44, 510.56 ng/mL, p < 0.00001) respectively. These serum ferritin values are shown in Figures 19, 20, and 21. In addition, one study [157] of the trials that contributed to this analysis reported a significant increase in serum ferritin in favor of IV iron group at day 5 and 4 weeks postoperatively (MD between groups: 757.55, 95 % CI: 556.47, 958.62 ng/mL, p < 0.0001), and (MD between groups: 396.92, 95 % CI: 260.45, 533.40 ng/mL, p < 0.0001) correspondingly. Another trial [156] showed a statistically significant rise in serum ferritin in favor of IV iron group at 4 weeks postoperatively. It was not possible to combine the data in the analysis because of its skewness. This trial reported their statists as median (IQR), which were 248 (137-546) ng/mL for IV iron versus 99 (35-228) ng/mL for control group, p = 0.002.

Figure 18: Forest plot comparison shows the pooled comparison of baseline value of ferritin levels (ng/mL) between intravenous iron therapy versus placebo/standard of care groups (random effects model).

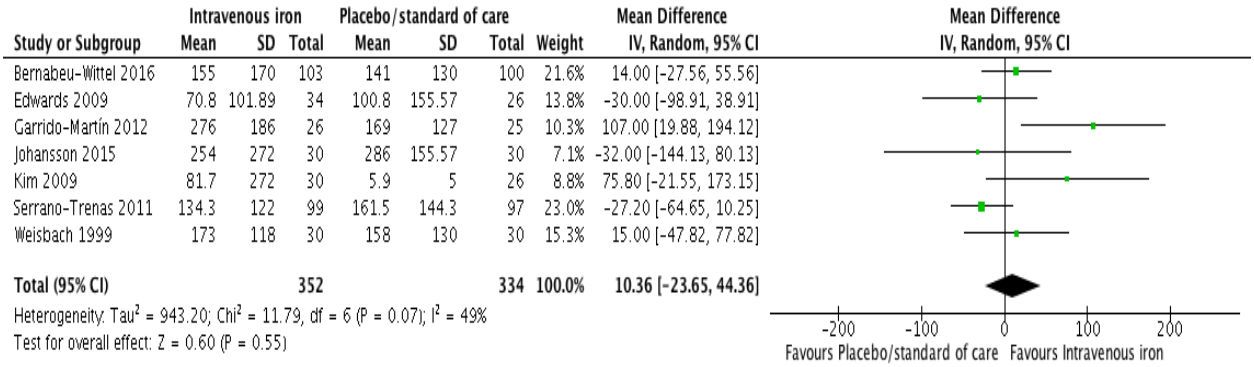


Figure 19: Forest plot comparison shows the pooled comparison effect of intravenous iron therapy versus placebo/standard of care on groups the ferritin levels (ng/mL) at the post-treatment (pre-surgery) time (random effects model).

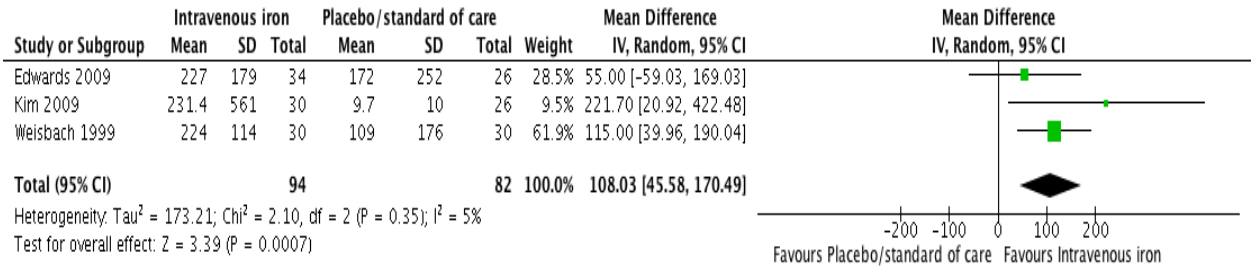


Figure 20: Forest plot comparison shows the pooled comparison effect of intravenous iron therapy versus placebo/standard of care groups on the ferritin levels (ng/mL) at the hospital discharge time (random effect model).

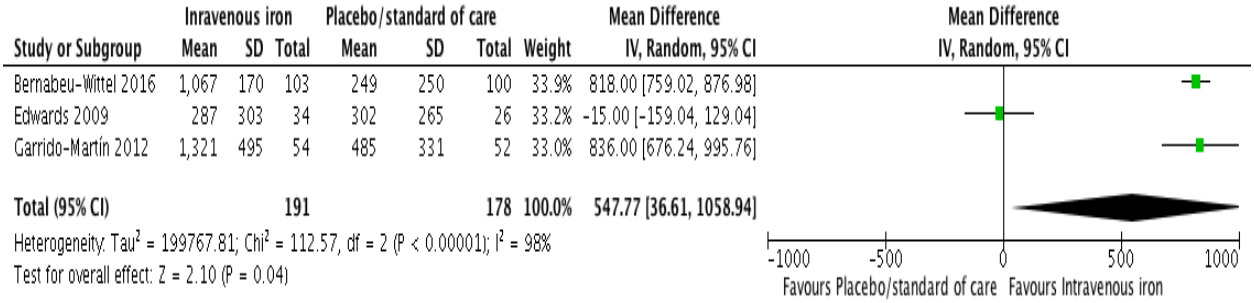
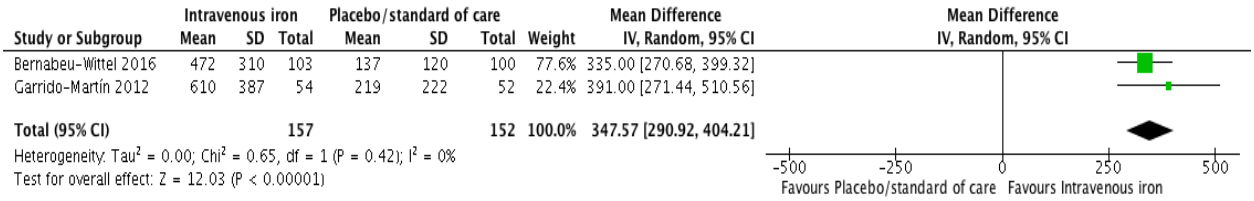


Figure 21: Forest plot comparison shows the pooled comparison effect of intravenous iron therapy versus placebo/standard of care groups on the ferritin levels (ng/mL) as follow-up > 4 weeks postoperatively (random effect model).



3.5.6. Transferrin saturation values (TSAT %)

Four studies [108, 130, 157, 159] of nine RCTs provided data about the change in the mean transferrin saturation level, which was similar at baseline (MD between groups: 0.92, 95% CI: -2.83, 4.86%, p = 0.63) as displayed in Figure 22. After IV iron treatment, TSAT % did not increase significantly neither when the participant were going to have their surgery (MD between groups: 6.36, 95% CI: -0.79, 13.51%, p = 0.08), nor at hospital discharge (MD between groups: -2.40, 95% CI: -7.85, 3.05%, p = 0.39), as revealed in Figures 23, and 24. Moreover, one study [157] of these four trials reported a significant increase in TSAT % in favor of IV iron group at day 5 and 4 weeks postoperatively (MD between groups: 12.60, 95 % CI: 9.70, 15.50 ng/mL, p < 0.0001), and (MD between groups: 6.52, 95 % CI: 2.65, 10.40 ng/mL, p < 0.002) correspondingly. A fifth study [156]showed a statistically significant rise in serum transferrin saturation in favor of IV iron group at 4 weeks postoperatively. It was not possible to include this trial data in the analysis because of its skewness. The investigators reported their data as median (IQR), which were 21 (16-26) % for IV iron versus 14 (7-18) % for control group, p = 0.003.

Figure 22: Forest plot comparison shows the pooled comparison of baseline value of the transferrin saturation value (TSAT %) between intravenous iron therapy versus placebo/standard of care groups (fixed effect model).

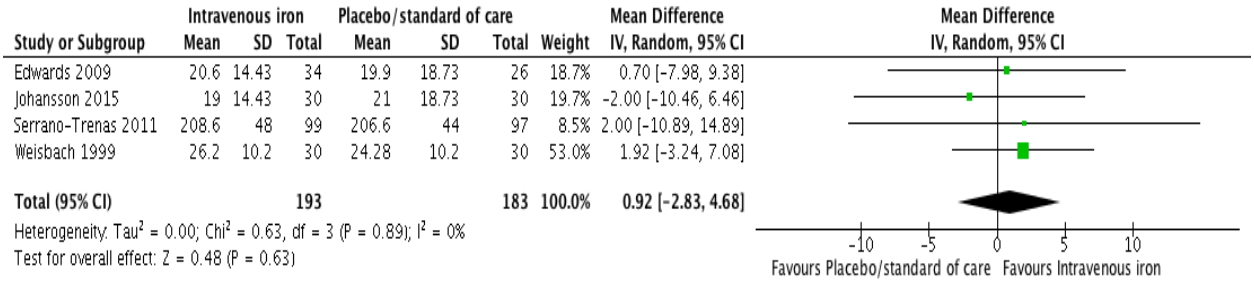


Figure 23: Forest plot comparison shows the pooled comparison effect of intravenous iron therapy versus placebo/standard of care groups on the transferrin saturation value (TSAT %) at the post-treatment (pre-surgery) time (random effects model).

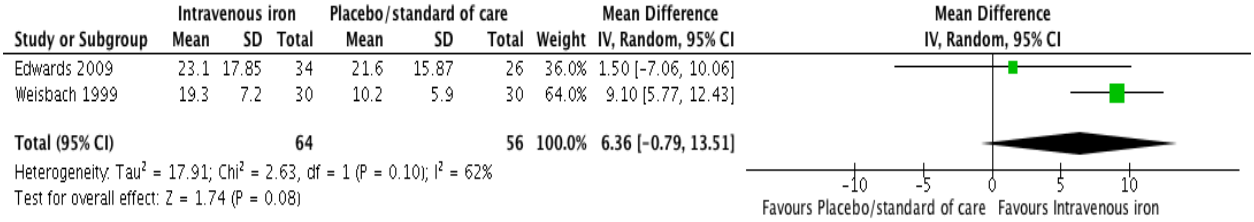
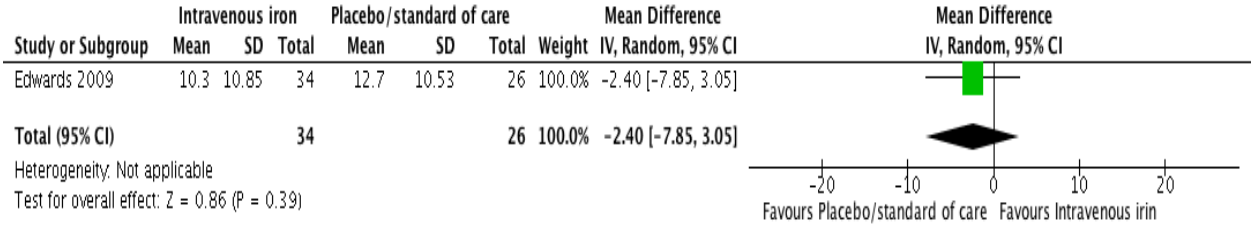


Figure 24: Forest plot comparison shows the pooled comparison effect of intravenous iron therapy versus placebo/standard of care groups on the transferrin saturation value (TSAT %) at the hospital discharge time (random effects model).



3.5.7. Reticulocyte percentage or counts

Two trials [129, 159] of the nine studies contribute to the analysis of the reticulocyte percentage at baseline where the reticulocyte percentages were equivalent in both groups (MD: -0.13, 95% CI: -0.41, 0.16%, P = 0.40) as shown in Figure 25. After the treatment with IV iron, only one study [159] provided data and IV iron injection was able to increase the reticulocyte percentage significantly at the pre-surgery time (MD between groups: 0.90, 95% CI: 0.33, 1.47%, P = 0.002) as shown in Figure 26. At hospital

discharge, one trial [129] reported a significant increase in the reticulocyte percentage in favor of the IV iron group (MD between groups: 0.30, 95% CI: 0.07, 0.53%, P = 0.01) as presented in Figure 27. This increase disappeared at one-month post-discharge (MD between groups: 0.20, 95% CI: -0.01, 0.41%, P = 0.06) as exhibited in Figure 28.

A third trial [157] reported data for the reticulocyte counts rather than percentage and this count was expressed as 10^9/L reticulocytes. In this trial, there was a significant increase in the mean difference of the reticulocyte count from baseline to day 5 in the IV iron group compared to placebo group (MD between groups: 16.20, 95% CI: 3.21, 29.18, P = 0.02). Later, there was no a significant change in the reticulocyte count from baseline to 4 weeks postoperatively (MD between groups: -4.85, 95% CI: -15.94, 6.24, P = 0.38).

Figure 25: Forest plot comparison shows the pooled comparison of baseline value of the reticulocyte percentage (%) between intravenous iron therapy versus placebo/standard of care groups (random effects model).

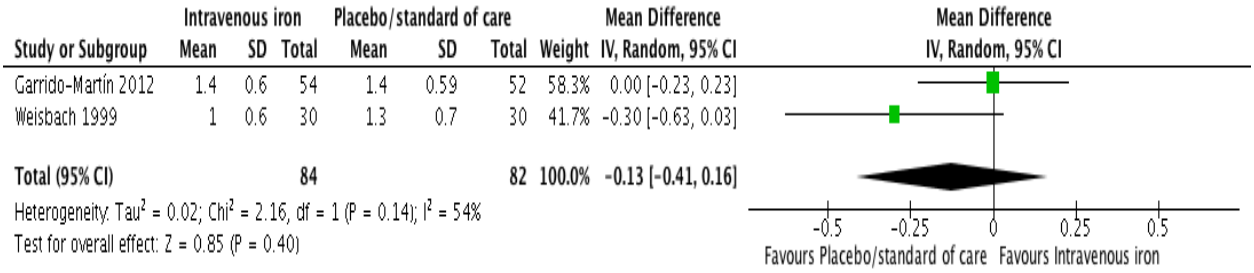


Figure 26: Forest plot comparison shows the effect of intravenous iron therapy versus placebo/standard of care groups on the reticulocyte percentage at the post-treatment (pre-surgery) time.

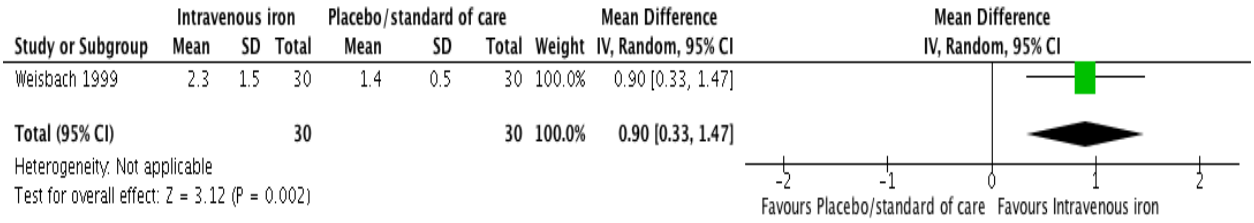


Figure 27: Forest plot comparison shows the effect of intravenous iron therapy versus placebo/standard of care groups on the reticulocyte percentage at the hospital discharge time.

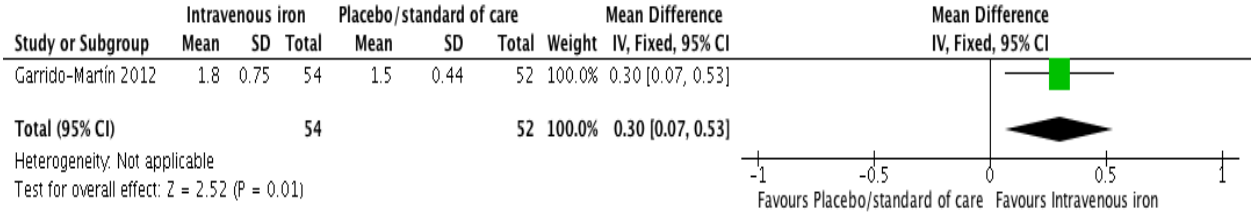
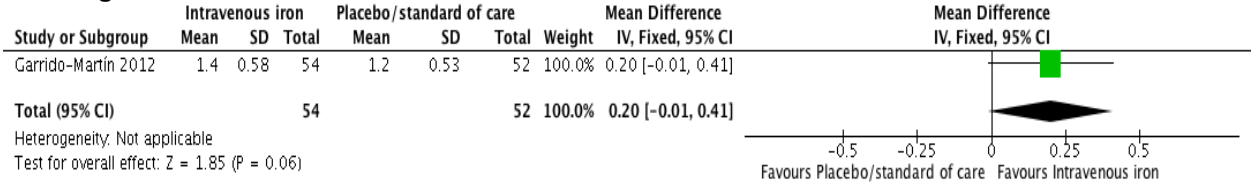


Figure 28: Forest plot comparison shows the effect of intravenous iron therapy versus placebo/standard of care groups on the reticulocyte percentage at a month from hospital discharge.



3.5.8. Mean corpuscular hemoglobin (MCH) level (pg/cell)

Two trials [130, 159] reported data for MCH, which was similar at the baseline level for both groups (MD: -0.35, 95% CI: -1.42, 0.73 pg/cell, P = 0.53) as revealed in Figure 29. After receiving IV iron and before going to surgery, there was no statistically significant difference between both groups (MD: 0.20, 95% CI: -1.56, 1.96 pg/cell, P = 0.82) as displayed in Figure 30.

Figure 29: Forest plot comparison shows the pooled comparison of baseline value of the mean corpuscular hemoglobin (MCH) level (pg/cell) between intravenous iron therapy versus placebo/standard of care groups (random effects model).

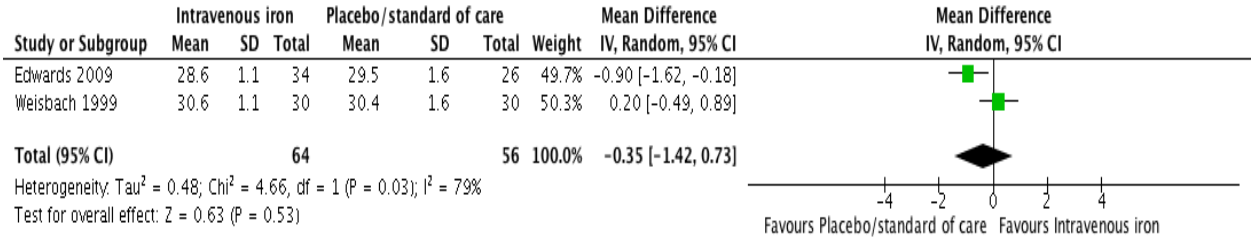
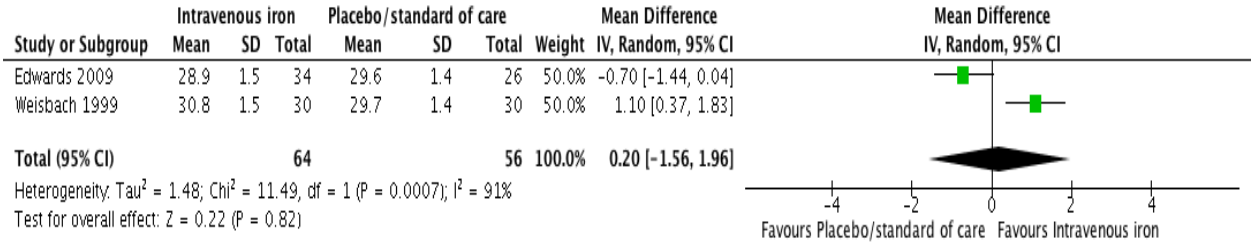


Figure 30: Forest plot comparison shows the pooled comparison effect of intravenous iron therapy versus placebo/standard of care groups on the mean corpuscular Hb (MCH) level (pg/cell) at the post-treatment (pre-surgery) time (random effects model).



3.5.9. Mean corpuscular hemoglobin concentration (MCHC) level (g/L)

Only one trial [155] reported data for MCHC at baseline that showed similar MCHC level in both groups (MD: -2.00, 95% CI: -17.14, 13.14 g/L, P = 0.80) as demonstrated in Figure 31. After administration of IV iron, at the pre-surgery time, a different trial [159] reported data for MCHC, which was similar for both arms (MD between groups: 2.00, 95% CI: -2.97, 6.97 g/L, P = 0.43) as demonstrated in Figure 32.

Figure 31: Forest plot comparison shows the comparison of baseline value of the mean corpuscular hemoglobin concentration (MCHC) level (g/L) between intravenous iron therapy versus placebo/standard of care groups.

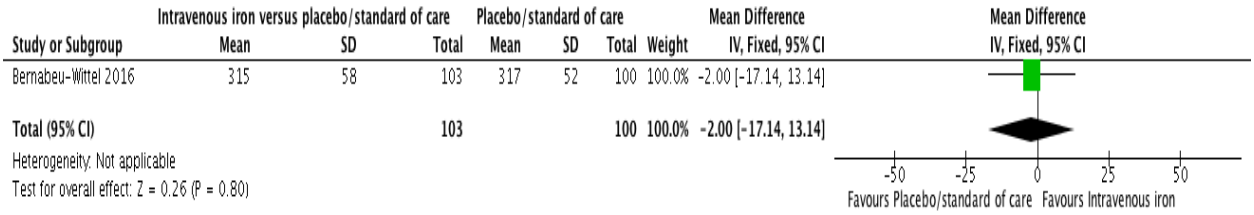
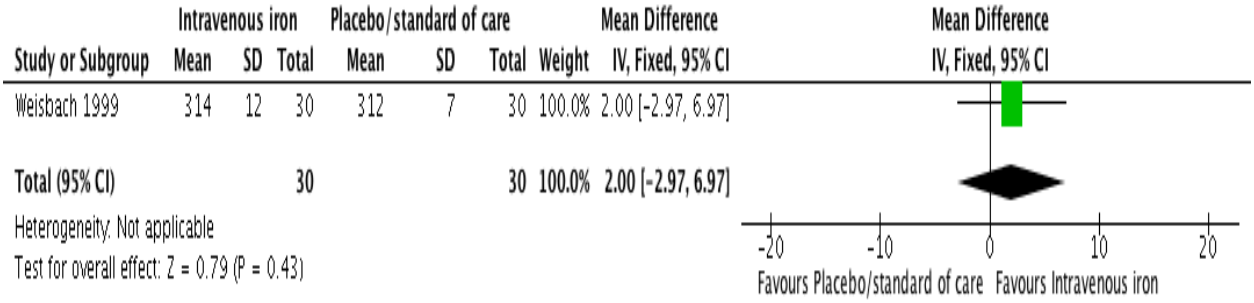


Figure 32: Forest plot comparison shows the effect of intravenous iron therapy versus placebo/standard of care groups on the mean corpuscular hemoglobin concentration (MCHC) level (g/L) at the post-treatment (pre-surgery) time.



3.5.10. Mean corpuscular volume or mean cell volume (MCV) level (fL).

Only one study [155] provided data at the baseline level that showed similar MCV values for both trial groups (MD: 0.90, 95% CI: -0.97, 2.77 fL, P = 0.34) as exhibited in Figure 33. After administration of IV iron, two trials [158, 159] described data for MCV, marked increases in the pooled MCV level was observed in favor of the IV iron group at the pre-surgery time (MD between groups: 6.67, 95% CI: 0.79, 12.54 fL, P = 0.03) as shown in Figure 34.

Figure 33: Forest plot comparison shows the pooled comparison of baseline value of the mean corpuscular volume (MCV) level (fL) between intravenous iron versus placebo/standard of care groups (random effects model).

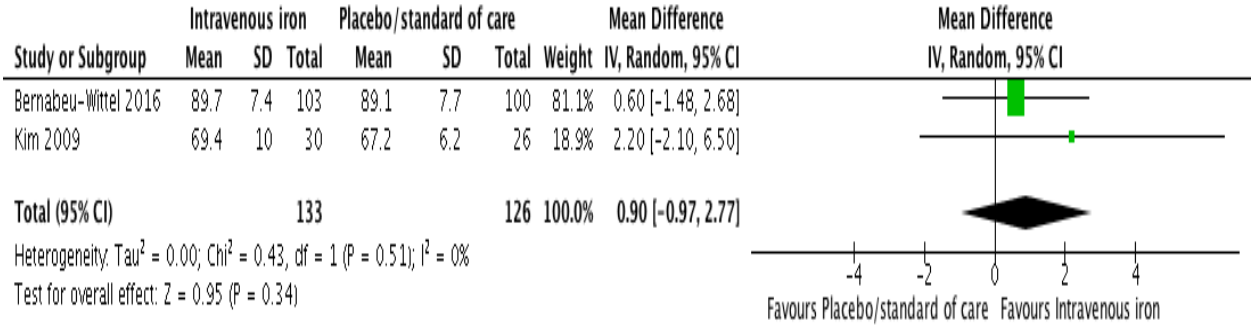
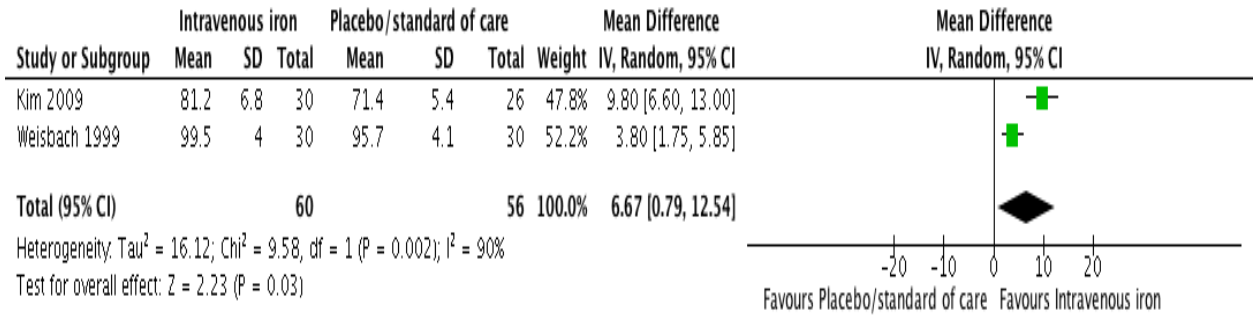


Figure 34: Forest plot comparison shows the pooled comparison effect of intravenous iron versus placebo/standard of care groups on the mean corpuscular volume (MCV) level (fL) at post-treatment (pre-surgery) time (random effects model).



3.5.11. Serum iron (μmol/l)

Two trials [108, 130] reported data on serum iron at baseline. Only one trial [130] provided data for serum iron after receiving IV iron treatment (at pre-surgery and at the hospital discharge), and there was no significant difference between the trial arms in the mean difference of the serum iron levels at any time point as revealed in Figures 35, 36, and 37. A third study [157] reported a significant increase in serum iron in favor of IV iron group at day 5 and 4 weeks postoperatively (MD between groups: 5.54, 95 % CI: 4.12, 6.96 ng/mL, P < 0.0001), and (MD between groups: 2.64, 95 % CI: 0.27, 5.07 ng/mL, P < 0.03) respectively.

Figure 35: Forest plot comparison shows the pooled comparison of baseline value of serum iron level (μmol/l) between intravenous iron therapy versus placebo/standard of care groups (random effects model).

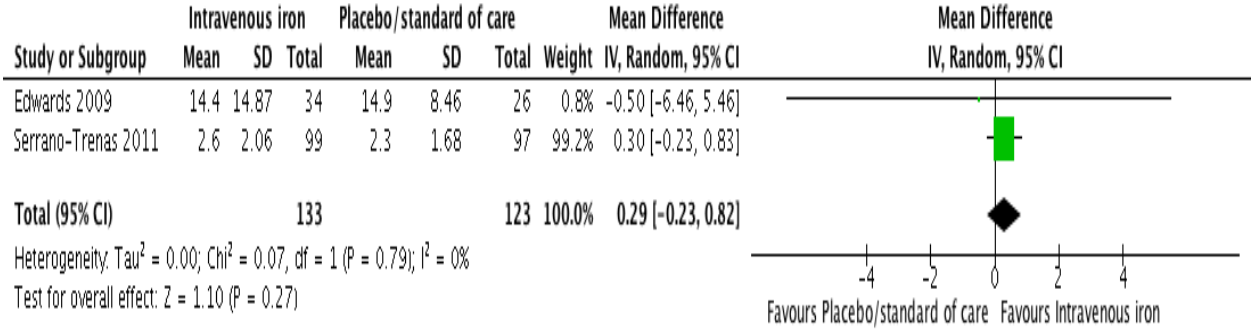


Figure 36: Forest plot comparison shows the effect of intravenous iron therapy versus placebo/standard of care groups on the change of serum iron level (μmol/l) at the post-treatment (pre-surgery) time.

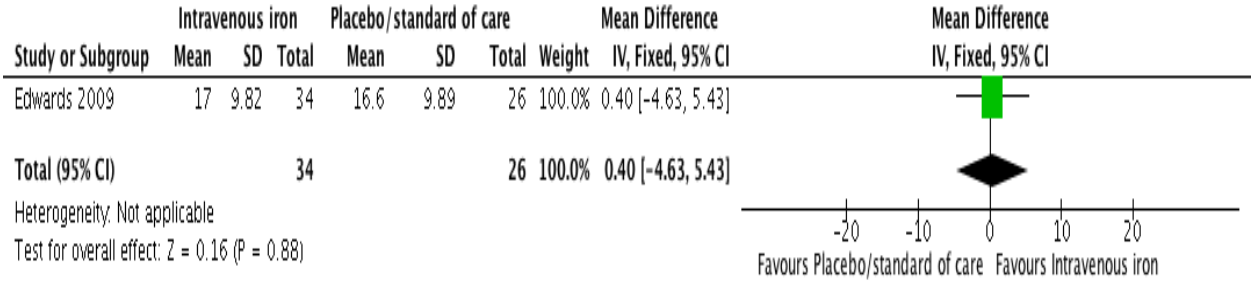
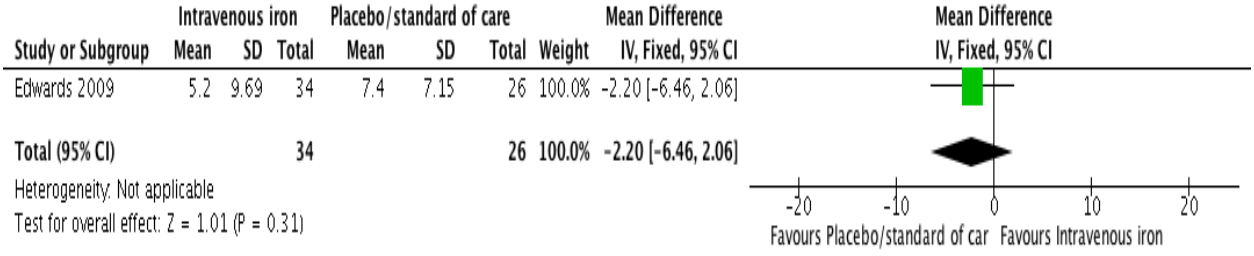


Figure 37: Forest plot comparison shows the effect of intravenous iron therapy versus placebo/standard of care groups on the change of serum iron (μmol/l) at the hospital discharge time.



3.5.12. Adverse events

The participants tolerated IV iron injection well, and most of the reported AEs were mild or moderate. For non-serious (mild or moderate) adverse reactions, eight of the nine trials [108, 129, 155-160] provided data. However, one trial [129] of these studies reported

zero events in both trial arms and another [157] did not report how many patients in each trial arm had non-serious AEs. Consequently, six studies [108, 155, 156, 158-160] contributed to the analysis. For the non-serious AEs, there was no difference between the two groups (RR: 1.17, 95% CI: 0.80, 1.71, p = 0.42) as shown in Figure 38. However, with including the trial of zero events, the results were similar (RR: 1.17, 95% CI: 0.80, 1.71, p = 0.42) as presented in Figure 39.

Regarding serious adverse effects (SAEs), only one [157] of the included trials reported SAEs, which were not drug-related. The incidence of these SAEs was similar in both groups (RR: 0.89, 95% CI: 0.40, 1.99, p = 0.77) as presented in Figure 40.

Figure 38: Forest plot comparison shows the effect of intravenous iron therapy versus placebo/standard of care groups on the on the occurrence of associated non-serious adverse effects (random effects model).

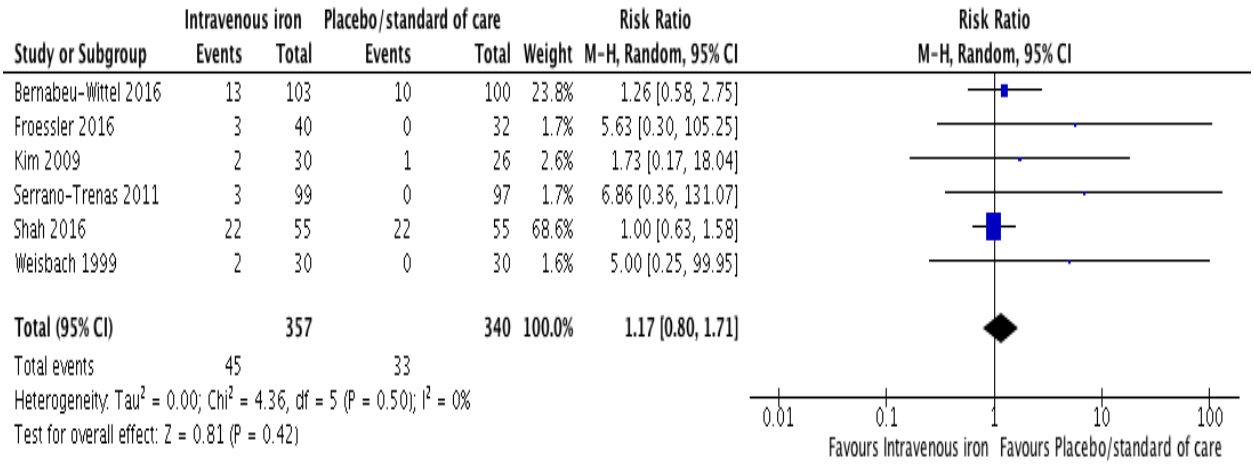


Figure 39: Forest plot comparison shows the effect of intravenous iron therapy versus placebo/standard of care groups on the occurrence of associated non-serious adverse effects after including a trial (Garrido-Martín et al.) with zero events (random effects model).

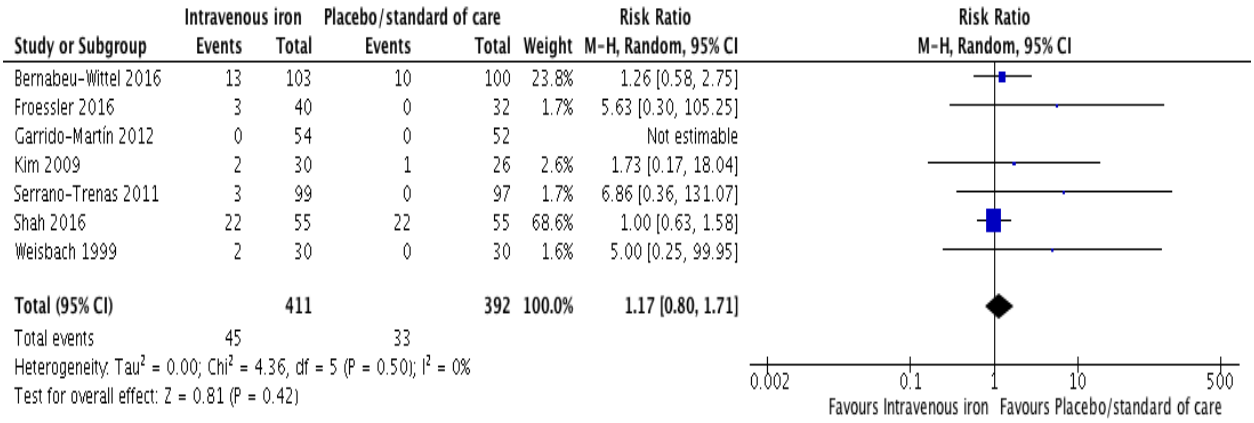
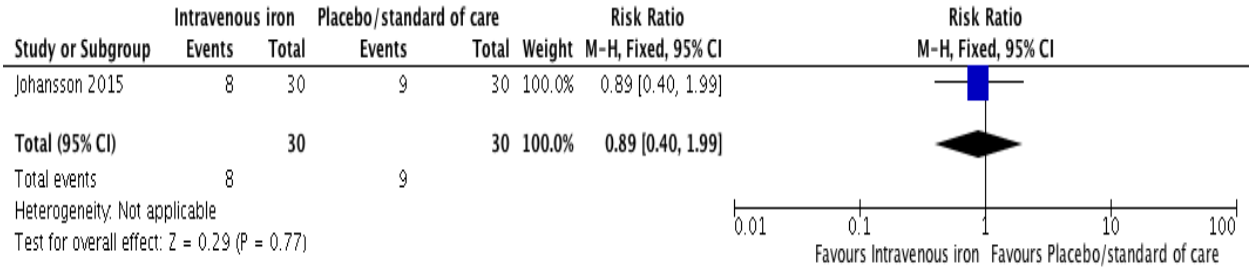


Figure 40: Forest plot comparison shows the effect of intravenous iron therapy versus placebo/standard of care on groups on the occurrence of associated serious adverse effects.



3.5.13. Mortality

Only four trials [108, 155-157] reported mortality data. One of these studies [157] had zero mortality across groups; so, three trials were included in the analysis. There was no statistically significant difference between the two groups for the reported 30-day mortality (RR: 1.29, 95% CI: 0.75, 2.22, p = 0.36) as shown in Figures 41. Similar results were obtained after including the trial of zero events (RR: 1.29, 95% CI: 0.75, 2.22, p = 0.36), and at two-month post-hospital discharge (RR: 1.26, 95% CI: 0.70, 2.38, p = 0.41) where one study [155] provide data as shown in Figures 42 and 43.

Figure 41: Forest plot comparison shows the pooled comparison effect of intravenous iron therapy versus placebo/standard of care groups on the 30-day mortality (random effects model).

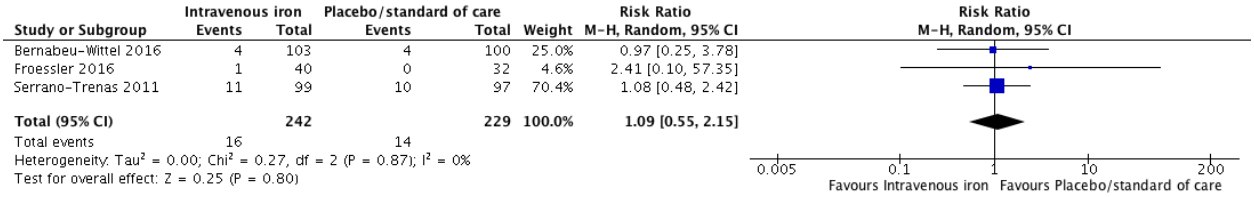


Figure 42: Forest plot comparison shows the pooled comparison effect of intravenous iron therapy versus placebo/standard of care groups on the 30-day mortality after including a trial (Johansson et al.) with zero events (random effects model).

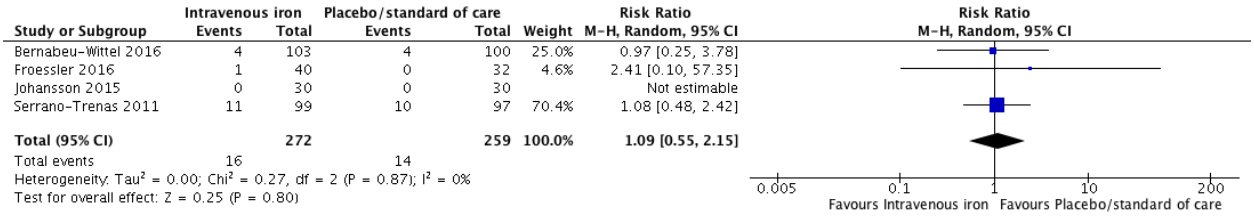
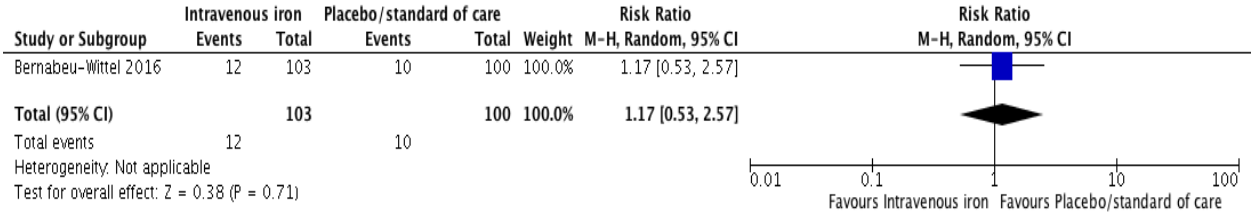


Figure 43: Forest plot comparison shows the effect of intravenous iron therapy versus placebo/standard of care groups on the mortality at two-month post-hospital discharge.

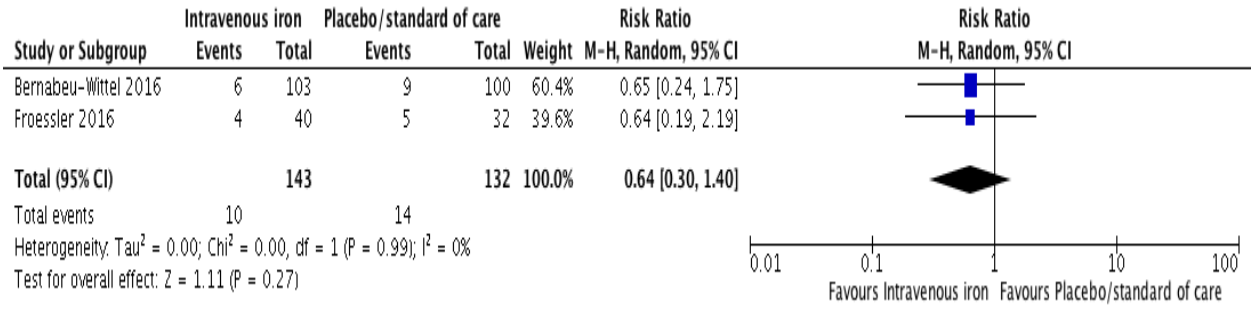


3.5.14. Infection

Four trials reported data for postoperative infection. One of these four studies [129] mentioned no increased infection rate between the trial arms but did not provide numbers. Another study [108] reported the total infection rate across the study (14.8%) but did not provide arm-specific numbers of infections. In that trial, the infection events reported were superficial surgical wound infections in eleven (5.6%) patients; deep surgical wound infections in two (1%) patients; respiratory infections in eight (4.1%) patients; and urinary infections in six (3.1%) patients. An additional two patients (1%) developed "other"

infections (diarrhea in one case and colorectal abscess in another patient). The other two studies [155, 156] showed similar infection incidence in both groups (RR: 0.64, 95% CI: 0.30, 1.40, p = 0.27) as exposed in Figure 44.

Figure 44: Forest plot comparison shows the pooled comparison effect of intravenous iron versus placebo/standard of care groups on the postoperative infection occurrence (random effects model).



3.5.15. Hospital length of stay

Four trials reported data about the hospital length of stay (LOS), although three of four studies provided the LOS as median days, and it was not possible to convert these medians to means and SDs, which RevMan software requires. However, only one trial [156] showed a shorter but not statistically significant LOS for the IV iron group with medians (minimum-maximum) LOS in IV iron group versus control group of 6 (1–19) versus 9 (1–23) respectively with P = 0·05. Similarly, the second, third, and fourth studies reported no differences between groups. The second trial' findings were reported as medians (first quartile-third quartile), which were 7 (5-10) for IV iron versus 8 (6-10) for control group [155]. The third trial' median LOS for IV iron group versus control group was

eight versus ten days respectively (P = 0·273) [130]. The fourth trial reported mean LOS of 13.5 ± 7.1 for IV iron group versus 13.1 ± 9.6 for the control group (P = 0·69)[108].

3.5.16. Quality of life

Health-related quality of life (HRQoL) data was provided in two only trials [155, 156]. These two trials used two different tests that make quantitative analysis not feasible to be conducted. In the first trial [155], the trial investigators used the Short Form 36 Version 2 for acute patients [SF-36v2] of the HRQoL [161] to assess their patients. The test was applied at baseline and 60 days after their hospital discharge. On the 60-day assessment, in the IV iron group, the patients' physical score summary decreased by a mean of 4.4 ± 14 versus 4.5 ±15 in the control group compared the baseline testing. For the study mental score summary, scores decreased by 2.7 ± 20 in the IV group and increased by 2 ± 20 in the control group compared to baseline testing. All these decreases/increases were statistically insignificant and clinically not important. With the second trial [156], the investigators used the Short Form Health Survey (SF36)[162] without specifying which version was conducted. Moreover, the authors used non-standard scoring of the test. The test was conducted at study entry and four weeks after their surgery. On four weeks post-surgery assessment, their two groups had very similar decreases in their scores (8 ± 18 versus 6 ± 17 in the IV iron and control groups respectively. However, similar to the first study, there was no statistically significant difference between arms.

3.6. DISCUSSION

The first core finding of this meta-analysis was a 17% reduction in the ABT for the participants who received IV iron therapy. Generally, in the clinical practice, the minimal clinical important difference (MCID) in a study has been defined as the smallest difference in an outcome treatment that a patient would recognize it as important and consequently would necessitate a shift in the patient's management [163]. For transfusion rate reduction, there is no cutoff has established as MCID. However, the largest currently ongoing trial to investigate the treatment of preoperative anemia using IV iron in major surgery used a risk reduction of 12 % in the transfusion rate as appropriate to calculate the sample size [164]. Accordingly, in this meta-analysis, it would seem that after receiving the IV iron, a reduction of 17% in the proportion of patients requiring ABT might considered clinically important and sufficient to change patient management.

In this meta-analysis, to investigate the trials' heterogeneity, subgroup analyses were conducted comparing cardiac versus non-cardiac surgeries settings that show no statistically significant difference between the subgroups regarding receiving a blood transfusion. However, to test the difference between the diverse IV iron preparations, only under the fixed effects model, the subgroup analysis showed that fewer patients received a transfusion in the iron sucrose trials compared to the carboxymaltose trials. This finding is of great benefit for patients, particularly Jehovah Witness (JW) patients where ABT is forbidden and other patients for whom transfusions are medically contra-indicated. This meta-analysis finding reinforces similar results previously found in a feasibility study [165], many observational studies [166-174], and a recent review. However, these findings may not be generalizable to patient populations other than those undergoing elective surgery. In particular, the findings from this meta-analysis conflict with a recent trial in critical care

patients [175] and a recent systematic review and meta-analysis [176] in the critical care setting. In the latter meta-analysis, findings were limited by considerable heterogeneity between trials including the nature of interventions and the risks of bias in the included studies. Moreover, in the current meta-analysis, participants underwent elective surgeries with ample time to receive IV iron injection to stimulate the erythropoiesis.

The second fundamental finding of my meta-analysis was the general trend of statistically significant increasing Hb levels. Interestingly, this increased tendency had a bi-phasic pattern composed of two waves, first, at the pre-surgery time, and second, at follow-up > 4 weeks postoperatively. The first weave existence before surgery is due to the effect of the early injection of iron (2-5 weeks before the operation) in some of the study trials. Interestingly, in the included trials of my meta-analysis, some of them started iron injection as early as of five weeks [159], at four weeks [160], at three weeks [158], or at two weeks [130] before the day of surgery. However, this initial wave disappeared immediately after surgery and throughout the hospital stay. This disappearance might be related to the attenuation/termination of the IV iron effect on the erythropoiesis in addition to the perioperative acute intraoperative blood loss including operative blood loss, repeated venipuncture to do blood tests, and blood loss through the surgical drains in the immediate postoperative stage.

The second wave that existed at four weeks after surgery indicates another new effect of the delayed IV iron administration by some trials or as an augmented effect of the pooled effect of early-injected iron by the other trials of the meta-analysis, which started their iron injection late (only 1-2 days around the surgery time). Those trials initiated their IV iron administration late either within two days of surgery [156], a day

before surgery or in the same day of surgery [157], or just before and after surgery [108, 129]. One of those trials [156] gave about a thousand gram of the IV iron 4-21 days pre-surgery in addition to extra-doses of IV iron (2mg of IV iron per 2 mL of blood loss, if blood loss was at least 100 mL) within two days post-surgery. Interestingly, this study was contributing a positive effect in the pooled estimate in both Hb rise waves. Overall, this observed Hb increase over time is in line with two feasibility studies [165, 177], several observational studies [167, 170, 178-180], two recent meta-analyses of the RCTs in iron-deficient patients [181] and in anemic patients with inflammatory bowel disease [182], in addition to a recent surgical trial that gave the IV iron postoperatively that showed an increase at 4 weeks postoperatively [183].

Of note, both waves of the Hb rise required about 4-week duration following the iron injection to exist either before or after surgery resulting in a statistically significant increase in the mean difference of the Hb level. This finding indicates that initiation of the iron injection is recommended to start at four weeks pre-surgery and to be continued till the surgery time to achieve a long effect of the IV iron to stimulate the erythropoiesis and to protect against ABT. This injection strategy timing will move the peak effect to be at the time of surgery and to continue for four weeks after surgery where the upturn from the acute blood loss is necessary for expedited patient recovery. The peak of the primary increase response in the Hb level has been shown to be around 3-4 weeks before starting to decrease over time as shown in another investigators' work [180]. Another finding of my study is the statistically significant rise in reticulocyte percentage/count after IV iron therapy, at 5 days postoperatively, and at the hospital discharge time demonstrating recent bone marrow activity in those participants receiving IV iron. Having an active bone

marrow at these time points implies that there was an active erythropoiesis just pre-surgery and throughout the hospital stay producing new Hb due to IV iron injection around the surgery time to prepare for the second wave of Hb rise in this meta-analysis.

It is of note that there was no significant increase in Hb levels in any of the three trials [108, 129, 130] in which the participants received a total dose equal to or less than 600 mg IV iron, which is at the lower end of the dosages used to treat anemia. Therefore, it is plausible that, with an increased IV iron dose, a significant enhancement in iron bioavailability may occur resulting in higher Hb levels preoperatively. The other observation was that in the two trials in which participants received a total dose more than a 1000 mg of IV iron [158, 160], the response was greater than in the trials using a total dose of a 1000 mg of IV iron [155-157]. Of note, these two trials that achieved greater response had younger patients, and all were female undergoing gynecological surgeries. As per the recent consensus, the recommended dose is between 1000 and 1500 mg of IV iron that can be infused slowly over less than one-hour in one or two divided doses contingent on the IV preparation given [184]. In very recent studies [167, 168], injecting IV iron between two and four weeks preoperatively was optimal timing, and was associated with a reduction in the RBC transfusion.

So, as per this pattern of positive dose-response relationship, it is reasonable to infer a causal relationship between administration of IV iron and improved Hb levels pre-surgery and after discharge. Although the increase in the Hb level difference is small, these results have substantial implications for treating physicians and the anemic patients, especially JW patients and those who are living in countries with restricted resources.

The included trials were heterogeneous in treatment dosage and sample size. Most of the included trials [155-158, 160] assessed large doses equal to or greater than 1000 mg of IV iron. In these five studies, IV iron administration in this dosage was safe. A recommendation for further research on this topic would be a well-designed clinical trial to precisely assess the value of administering a higher dose of IV (e.g., 1000-1500 mg) and initiating this treatment at four weeks preoperatively followed by extra-doses before the operation. This kind of study would test the hypothesis that an optimally timed IV iron administered in large dose preoperatively will be safe and will counteract acute blood loss associated with major surgery. If the trial were powered to the transfusion reduction target with positive results, this would show that while anemia is a common complication around major surgery, a higher dose of IV iron therapy is a safe, feasible, convenient to the surgical patient and this may be a cost-effective strategy to minimize ABT as well, but such work has not yet to be performed. Furthermore, although none of the included studies reported cost-effectiveness data, it is likely that preoperative treatment with IV iron, in comparison with repeated transfusions, is an affordable option in developing and under-developed countries where preoperative anemia is very common.

Findings related to the Hb increase should be interpreted cautiously. One of the trials showing positive result [158] has a high risk of bias. In this study, although about a quarter of the participants in each arm had a similar history of previous iron treatment, a large proportion of participants (80%) were excluded because of poor compliance, which may lead to selection bias. Nevertheless, a sensitivity analysis excluding this trial showed a similar and still statistically significant effect size.

Interestingly, the rise in Hb concentration was significantly associated with lower exposure to ABT. However, in sensitivity analysis excluding a trial [159] designed mainly to evaluate the capability of IV iron administration to reduce any autologous blood donation perioperatively, IV iron therapy showed more significant benefit in minimizing the ABT. Moreover, most of the included trials in the meta-analysis had a small sample size and were not adequately powered to detect a diminution in transfusion rates. However, a combination of these small sample sized trials will obtain enough power. Another possible reason for this finding may be that in three [108, 129, 130] of the included nine trials; the participants received a dose equal to or less than 600 mg of IV iron. This is a low dose and arguably could have been increased safely to achieve higher Hb levels that protect against ABT.

In addition to the reduction in ABT needs and the rise in the Hb concentration in the IV iron group, this meta-analysis shows a substantial increase in the serum ferritin level as the principal iron storage parameter to support the benefit of a preoperative IV iron administration strategy to treat preoperative anemia. So, participants who received IV iron demonstrated more rapid correction of iron stores depletion than those in the control group. This ferritin level rise in the IV iron group was significant at every time interval during the hospital stay and after discharge. This demonstrates the better efficacy of IV Iron to correct the iron deficiency (ID) pre-surgery than the control group and to replace the ongoing iron losses perioperatively. This growth in the ferritin level reflected on the increase in Hb levels as well. It is not surprising that the peak of the ferritin increase at hospital discharge preceded the second wave of the Hb rise (at four-week

postoperatively). This is due to the fact that iron replenishment is a process that happens prior to Hb formation.

These data support other investigators findings [180], which demonstrated a significant increase of the serum ferritin with the use of IV iron therapy to correct anemia before elective surgery.

Concerning the other iron parameters in the meta-analysis, findings for TSAT %, which is the primary iron source for erythropoiesis and serum iron, indicate that these two parameters did not change significantly after IV injection, which supports the findings of two observational studies trials [172, 180].

I did not find a significant difference in postoperative AEs occurrence between the group receiving IV iron versus the group receiving placebo or oral iron. This finding confirms those of another study [185]. Concerns have been raised about the possibility of an increased incidence of AEs when IV iron is administered in larger than standard doses [186]. However, the pooled analyses on non-serious AEs, which included six of nine trials, did not show any statistically significant difference between the two groups in this meta-analysis. Moreover, subgroup analyses comparing low versus moderate doses of IV iron showed no significant difference in the occurrence of AEs indicating well-toleration of its administration. However, in one trial [159] of those studies, two of thirty patients in the IV iron group were excluded due to AEs or intolerance. Only one study [157] reported numbers for the serious AEs to be analyzed. This study finding revealed that there was no significant difference in the occurrence of life-threatening AEs between the patients receiving IV iron and those did not receive it.

The chief AEs related to IV iron administration were erythema with pain/itching at the injection site, phlebitis, discomfort, fever, and dizziness. In the participants who received oral iron, nausea, vomiting, constipation, and diarrhea were more frequent. Interestingly, hypophosphatemia as a side effect associated with injection of a high dosage of IV iron, which requires checking the serum phosphate before and after the therapy was not mentioned in any of the included trial except one study [157] in which all the participant received a single dose of 1000 mg of IV iron isomaltoside but there was no any participant had a serum phosphate level <2 mg/dl during therapy.

Given the relatively small sample size of each trial and the relative rarity of serious side effects as the anaphylactic shock reactions, there is a need for a large-scale phase III clinical trial to provide definitive answers about the frequency of serious AEs. Also, a large observational study will be of help to study the incidence of the AEs of IV iron. However, according to the United States Death Certificate Registry, only three mortalities were coded as "AEs in therapeutic use of iron preparation" over the period between 1979 and 2006 [187].

In this meta-analysis, the 30-day mortality was similar for the meta-analysis groups. Also, the infection rates were similar, providing evidence that IV iron is a safe therapy.

None of the incorporated trials reported data for cost-effectiveness making an economic analysis difficult to assess the cost aspects of IV iron in preoperative anemia management.

For quality of life, only two out of the nine trials provided data. Unfortunately, these two studies used different scaling tests and could not be pooled. However, neither study displayed a statistically significant difference.

This meta-analysis has relatively a small sample size because of the relatively restricted inclusion/exclusion criteria, which resulted in only nine trials included, all of which had a limited number of participants. Moreover, the global influence of IV iron administration in the subgroup of surgical patients requires a larger scale, phase III randomized clinical trial to explore the optimal dose, timing, which IV iron preparation has better efficacy, and safety to specify ultimate replies for many clinical questions.

Based on these results, I recommend clinicians to keep exerting all efforts to use IV iron to avoid the associated risks of ABTs. Since the available data on IV iron usage are limited, these meta-analysis findings have significant implications for patient care in the major surgery setting, particularly in JW patients, those for whom ABTs are medically contraindicated, and patients in countries with limited resources, which accounts for most of the globe nations.

Strengths of the study

This meta-analysis has many methodological strengths. The meta-analysis search was comprehensive without having any time, language, and IV iron preparation restrictions. All analyses were performed using both fixed-effect and random-effect models. This is a strength since both techniques deliver very similar results in the absence of heterogeneity when there is between-study heterogeneity, both techniques may be biased, random-effects models will be more conservative [188]. Thus, being able to

compare findings from both random and fixed-effects models provides the reader with more information.

As a systematic review and meta-analysis of the RCTs that showed a statistical significance and a clinically effective treatment of the effects of IV iron to reduce ABT will provide high-quality evidence base to estimate the treatment efficacy with more precision than it is possible in a single previous study and to add more to the existing evidence base to support implications for practice and having very useful decision-making tools.

Limitations of the study

This meta-analysis has some limitations. The first limitation is the fact that some of the included studies recruited non-anemic patients, which would bias their findings toward the null. Second, the current study findings may not be generalizable to younger patients undergoing major surgery since seven of the nine trials had mean/median age above 64 years old. Thus, these findings may be valid only in elderly patients. Only the two gynecological studies investigated younger female patients experiencing menorrhagia; a condition that usually exists at a younger age. Consequently, the results of the meta-analysis may not apply to young male patients, or younger female patients not experiencing menorrhagia. A third potential limitation of this meta-analysis is the relatively smaller sample size of most of the trials that necessitates careful interpretation of the reported side effects of IV iron since larger studies are needed to identify any but the most common side effects. The fourth limitation is that I estimated and imputed SD for trials when these were not published. This could be a source of bias, although the alternative would have been to exclude those trials. Doing so would have resulted in a

smaller sample size of this meta-analysis and would have introduced another kind of bias that would have made the interpretation of findings difficult. As per The Cochrane handbook of systematic reviews recommendation in meta-analyses with a small number of trials [151], I did not draw a funnel plot to explore publication bias because I had only nine trials.

3.7. CONCLUSION

The meta-analysis results provided evidence in support of the preoperative intravenous iron administration to increase hemoglobin level at pre-surgery, which was sufficient to significantly reduce the likelihood of allogeneic blood transfusion in patients undergoing major surgery.

Future directions

Since no single study of the included trials provided the definitive understanding of responses to intravenous iron therapy, additional full-scale clinical trials at a low risk of bias are still required to give definitive answers for the efficacy, safety and to provide evidence of cost benefits and quality of life after injection of intravenous iron in preoperative anemia correction. Those new trials have to test the newly intravenous iron preparations that contain more iron per injection to minimize the blood transfusion in patients undergoing elective major surgery.

To overcome the limitations of single trial conduction, future meta-analysis conduction is recommended where it will be more valuable than any single study contributing to the analysis. Undertaking a consequent meta-analysis will include diverse

populations allowing for additional subgroup analyses for different surgery to address the effect of the influencing disease and to find if any particular iron preparation provides more efficacies. Doing this subgroup analysis might offer the opportunity to evaluate new hypotheses.

CHAPTER IV (PAPER-III): OPTIMIZING PREOPERATIVE HEMOGLOBIN IN ADULT CARDIAC SURGERY USING INTRAVENOUS IRON SUCROSE (VENOFER): A CASE SERIES

4.1. ABSTRACT

4.1.1. Background

Perioperative anemia is a common and potentially serious hematological problem in adult patients undergoing elective cardiac surgery. This anemia is associated with increased risk of perioperative red blood cell transfusion. Transfusion is associated with more frequent postoperative morbidity and mortality. Preoperative intravenous iron sucrose (Venofer) therapy has been suggested as one therapeutic intervention to reduce perioperative transfusion.

4.1.2. Objective

To investigate the effect of preoperative intravenous (IV) iron sucrose as a prophylactic iron therapy to reduce the receipt of allogeneic blood transfusion in adult patients scheduled for elective cardiac surgery

4.1.3. Patients and Methods

This retrospective observational case series was carried out at the University of Alberta Hospital between January 2010 and December 2015. This study included 31 consecutive patients who were treated with intravenous iron sucrose as monotherapy to

increase their hemoglobin (Hb) level and to minimize allogeneic blood transfusion. Treatment efficacy was analyzed based on the Hb value rise and the rate of allogeneic blood transfusion.

4.1.4. Results

A total of 31 patients received IV iron sucrose with an average dose of 584 mg (range: 300-1000mg) of IV iron sucrose were given. After IV iron treatment, mean Hb level increased significantly from 125.70 ± 11 g/L at baseline to be 132.30 ± 16 g/L at the time of surgery with p = 0.007, with mean difference of 6.6 g/L (95% confidence interval [CI]: 2.00, 11.11 g/L). Moreover, depleted iron stores were restored, and serum ferritin level increased significantly from 25.43 ± 18.47 ng/mL at baseline to be 239.80 ± 18.47 ng/ml at surgery (p = 0.004). Allogeneic perioperative red blood cell transfusion occurred in 9 (29%) patients, which is lower than the latest largest Canadian report in 2012 on adult cardiac surgery

4.1.5. Conclusion

In patients undergoing elective cardiac surgery, IV iron sucrose administration led to an increase in the Hb level before patients underwent surgery. It was associated with a significant increase in ferritin levels and reduction in RBCs transfusion compared with the overall Canadian allogeneic blood transfusion.

4.2. INTRODUCTION

The etiology of perioperative anemia in adult patients undergoing cardiac surgery is usually multifactorial. Unavoidable acute intraoperative blood loss, early post-surgery

bleeding through the mediastinal/chest tube drainage and repeated phlebotomies are the principal causes. Moreover, some patients require pre-surgical coronary angiography, anticoagulation, or antiplatelet agents therapy that aggravate the condition. Perioperative anemia is associated with increased probability of receiving perioperative red blood cells (RBCs) transfusion [78]. Currently, allogeneic RBCs transfusions remain the standard of care to treat anemia, particularly in surgical patients with moderate-to-severe anemia [189]. In a recent large study of patients undergoing isolated on-pump cardiac surgery, after propensity-adjusted analysis, receiving as little as one or two units of RBCs was significantly associated with increased mortality (odds ratio [OR] 1.86), acute kidney injury (OR 2.63), reoperation for bleeding (OR 6.24), mechanical ventilation time (OR 2.34), and increased hospital length of stay (LOS) postoperatively (OR 2.16) [98]. Moreover, transfusion is a costly process to manage perioperative anemia. The cost for each RBC unit has recently been estimated at between US $522 and US $1,183 after including direct and indirect expenses [101].

Typically, patients' requirement for perioperative ABT is multifactorial. It depends mainly on the pre-surgery hemoglobin (Hb) concentration reflecting the RBCs mass of the circulating blood, the perioperative blood loss volume, and the institutional transfusion trigger. It has been reported that major surgery is usually associated with increased systemic inflammatory response resulting in inhibited erythropoiesis by the overflow of humoral mediators [30]. Successful strategies to avoid perioperative transfusion include correction of perioperative anemia and optimizing the Hb concentration through maximizing hemopoiesis preoperatively. Moreover, former investigators reported that even in non-anemic patients who are undergoing major surgery with expected significant

blood loss, receiving iron therapy might help in recovery from perioperative anemia [112]. However, in the recent international consensus to manage perioperative anemia, they recommend achieving of Hb level ≥ 130 g/L for both genders before going for surgery to avoid the risks of ABT [184].

The pathophysiology of perioperative anemia in cardiac surgery is mainly iron deficiency (ID) caused by blood loss in addition to the reduced nutritional intake chiefly in the early postoperative period. This condition could be cured through a bloodless therapeutic modality to avoid the transfusion risks. Accordingly, replenishing exhausted iron stores before surgery to optimize Hb level is considered an appropriate treatment [190]. Compared to oral iron, intravenous (IV) iron has a large quantity of iron that can be given over a few numbers of doses with excellent bioavailability for erythropoiesis [140]. In addition, it has fast uptake by bone marrow as demonstrated by positron emission tomography in another study [141]. Moreover, oral iron is a time-consuming therapy, which is unacceptable for most of the patients who need cardiac surgery. IV iron has been shown to accelerate the erythropoiesis to counteract anemia resulted from perioperative blood loss [191]. Therefore, these physiological properties of IV iron could result in a faster bloodless curative modality of perioperative anemia.

This study aimed to describe the outcomes of a group of patients who received preoperative IV iron as a strategy to counteract the acute blood loss to reduce allogeneic RBCs transfusion.

4.3. PATIENTS AND METHODS

After obtaining approval from my institutional review ethical board (REB #: Pro00045780) to waive the need for patient consent (Appendix 7), a retrospective search of my institution's electronic database was performed to identify the adult patients (between January 2010 and December 2015) who underwent cardiac surgery with Hb level at least 100 g/L, serum ferritin < 70 ng/mL, and consequently, received IV iron sucrose preoperatively. The reason for choosing the Hb cut-off value of 100 g/L before the administration of IV iron was to identify those cases whose Hb levels were likely to benefit from the intervention but to exclude patients who were severely anemic since those patients were likely to require RBC transfusion. The included patients received IV iron to optimize their Hb level within 2-3 months pre-surgery, with the goal of minimizing allogeneic blood transfusion (ABT). This study was undertaken at the blood conservation clinic established in my institution since 2010 to use IV iron as a strategy to reduce allogeneic RBC transfusion in the treatment of perioperative anemia.

Patients' data were collected from the institution electronic records and patients' charts. Patients who were under age of eighteen years, had liver diseases, had hemochromatosis/hemosiderosis, had ongoing infection/atopy, had an allergy to iron products, or received transfusion within 120 days before receiving IV iron sucrose were excluded from the case series.

Patients' baseline characteristics, including their demographical and clinical data, were recorded on a data extraction form. This included: age, sex, body mass index (BMI), type of scheduled surgical procedure, Hb levels (at baseline, post-Venofer treatment, the early postoperative time and hospital discharge time), ferritin levels (at baseline and post-Venofer treatment), and concomitant risk conditions/comorbidities at the time of surgery.

Also collected and recorded were: total cardiopulmonary bypass time, cross-clamp time, transfusion requirement data, the cardiovascular intensive care unit (CVICU) length of stay (LOS), the hospital LOS, and 30-day mortality were recorded. The primary outcomes were Hb concentration change and allogeneic RBCs transfusion rate. Secondary outcomes of interest were serum ferritin level change, the total number of transfusion events, the number of RBC transfusions/patient, acute kidney injury, infection, mortality within 30 days of surgery, and the hospital LOS.

4.3.1.1. Statistical analysis

Continuous variables were presented as means ± standard deviation (SD). Paired student t-tests were used to compare changes in Hb values and serum ferritin levels at different time points. Unpaired student t-tests were used to assess the differences in Hb concentration, serum ferritin values, and hospital LOS between who were transfused and those who did not receive a blood transfusion. Dichotomous variables were expressed as numbers (percentage). Subgroup analyses for who get transfused and who did not receive blood were done to investigate if there was any association between the Hb/ferritin values and receiving a; blood transfusion. A p-value < 0.05 was set for statistically significance. All data were analyzed using the SPSS® version 20 (IBM, Armonk, NY, USA).

4.4. RESULTS

Over a six-year period, 31 consecutive patients (11 [35%] males, 20 [65%] females) met the inclusion criteria, with age range of 18-70 years. These patients were

relatively young (mean age of 38.3 ± 21.29 years) at the time of surgery and had a mean body mass index (BMI) of 28.03 ± 7.30 kg/m2. Prior to surgery, eight (26%) patients had hypertension, eleven (35%) patients had hyperlipidemia, two (6%) patients had type I diabetes mellitus, seven (23%) patients had type II diabetes mellitus, eight (26%) patients were current or former smokers, two (6%) patients had a history of cerebrovascular events, no patient had prior myocardial infarction, peripheral vascular disease or was on renal dialysis prior to surgery and six (19%) patients had percutaneous coronary intervention (PCI) prior to surgery (Table 3).

Table 3: Preoperative patients' characteristics

Variable	*Number (%)/mean ± standard deviation*
Age (years)	38.63 ± 21.29
Female sex	20 (65%)
Body mass index (kg/m2)	28.03 ± 7.30
Hypertension	8 (26%)
Hyperlipidemia	11 (35%)
Diabetes (type I)	2 (6%)
Diabetes (type II)	7 (23%)
Smoking (current or former)	8 (26%)
Cerebrovascular events	2 (6%)
Prior myocardial infarction	0 (0%)
Peripheral vascular disease	0 (0%)
Renal dialysis	0 (0%)
Percutaneous coronary intervention	6 (19%)

Continuous variables are presented as means ± standard deviation; categorical variables are presented as number (%).

All patients (Table 4) had elective surgery; twenty-one (68%) patients were undergoing cardiac surgery for the first time, and ten (32%) patients had cardiac surgery for the second time. In the same table, it shows the different indications for surgery, cross-clamp time, pump run time, the mechanical ventilation time, CVICU stay, total hospital LOS, and the early postoperative outcomes (Acute kidney injury, stroke, and postoperative infection).

Table 4: Perioperative profile.

Variable	*Number (%)/mean ± standard deviation*
Redo cardiac surgery	10 (32%)
Isolated CABG surgery	14 (45%)
Isolated valve surgery	5 (16%)
Combined CABG and valve surgery	7 (23%)
Adult congenital surgery (ASD and VSD repair)	5 (16%)
Cardiopulmonary bypass time (minutes)	137.46 ± 78.18
Cross-clamp time (minutes)	80.68 ± 69.12
Prolonged mechanical ventilation >24 hours.	2 (6%)
CVICU length of stay (hours)	51± 22
Total hospital length of stay (days)	9 ± 3.6
Acute kidney injury	0
Stroke	0
Postoperative infection	0

Continuous variables are presented as means ± standard deviation; categorical variables are presented as number (%). CABG = coronary artery bypass grafting; ASD = atrial septal defect; VSD = ventricular septal defect; CVICU = cardiovascular intensive care.

After administration of IV iron sucrose, there was a significant increase in the Hb level at the pre-surgery time. At baseline, the mean Hb level was 125.70 ± 11 g/L, which increased significantly to 132.30 ± 16 g/L before going for surgery (Table 5). The mean increase was 6.6 g/L (95% confidence interval [CI]: 2.0, 11.10 g/L, p = 0.007). In the early postoperative period, Hb concentration dropped quickly and significantly. This drop reaches a statistically significant value compared to the pre-treatment level. The value of Hb was 103.66 ± 11 g/L at post-surgery with a mean difference of -22.04 g/L (95% CI: -16.0, -28.08 g/L, p < 0.0001) compared to the baseline values. Similarly, at hospital

discharge, Hb level had decreased significantly compared to the baseline level to be 99.59 ± 14.3 g/L with a mean difference of -26.11 g/L (95% CI: - 20.0, -32.22 g/L, p < 0.0001).

In addition to the Hb increase preoperatively, the IV iron sucrose injection replenished the iron stores. Consequently, the serum ferritin increased significantly from 25.43 ± 18.47 ng/mL at baseline level to 239.80 ± 18.47 ng/mL at the pre-surgery time with mean growth difference of 214.37 ng/mL (95% CI: 82.73, 346.01 ng/mL, p = 0.004).

Table 5: Hemoglobin, ferritin values, and transfusion data

Variable	***Number (%)/mean ± standard deviation***
Initial hemoglobin level (pre-treatment)	125.70 ± 11 g/L
Hemoglobin level at surgery (post-treatment)	132.30 ± 16 g/L
Hemoglobin level after surgery	103.66 ± 11 g/L
Hemoglobin level at hospital discharge	99.59 ± 14.3 g/L
Mean increase difference from baseline to pre-surgery time for the hemoglobin level	6.6 g/L (p = 0.007)
Mean increase difference from baseline to post-surgery time for the hemoglobin level	-22.04 g/L (p < 0.0001)
Mean increase difference from baseline to hospital-discharge time for the hemoglobin level	-26.11 g/L (p < 0.0001)
Serum ferritin level at baseline level	25.43 ± 18.47 ng/mL
Serum ferritin level at pre-surgery time	239.80 ± 18.47 ng/mL
Mean increase difference from baseline to pre-surgery time in the serum ferritin level	214.37 ng/mL (p = 0.004)
Transfused patients	9 (29)
Total number of transfusion events	36
Units transfused/patient (mean, minimum–maximum)	(4, 1-7)

Hb level measurements at different time points for the subgroup of patients who were transfused versus those who do not are summarized in Table 6. There was no statistically significant difference between the patients who received and who did not receive blood in the means of Hb concentration at baseline, at pre-surgery, or in the post-operative period. Similarly, there was no statistically significant difference in perioperative serum ferritin between the patients who received and who did not receive blood, and the hospital LOS was equivalent between the two subgroups. In this study, nine (29%) patients received RBCs. The total number of transfusion events was 36 occasions, and the total units/transfused patient (mean, minimum–maximum) was (4, 1-7). There were no acute kidney injuries, stroke, or postoperative infection in this case series.

Table 6: Subgroup analysis between transfused and non-transfused patients.

Variable	Non- transfused patients	Transfused patients	P-value
Hemoglobin level at baseline (g/L)	126.6 ± 107	123.6 ± 141.6	0.6
Hemoglobin level at pre-surgery (g/L)	134.2 ± 153.7	12.76 ± 184.0	0.3
Hemoglobin level at post-surgery (g/L)	104.9 ± 113.7	102.3 ± 102.5	0.6
Serum ferritin level at pre-surgery (ng/mL)	189.33 ± 134.00	252.42 ± 264.74	0.6
Total hospital length of stay (days)	10.00 ± 6.08	7.67 ± 2.69	0.3

4.5. DISCUSSION

The first critical observation in this study was the statistically significant increase in the pre-surgical Hb levels compared with pre-treatment baseline values after IV iron

treatment, reflecting a strong effect of IV iron sucrose to enhance erythropoiesis. The average increase in Hb levels was 6.6 g/L, which was sufficient to bring male patients in the study from the status of being anemic to being non-anemic as per the World Health Organization (WHO) definition of anemia [6]. Also, it was found that the introduction of the IV iron sucrose was also associated with rapid replenishment of the iron stores as indicated by the significant rise in the mean ferritin level before going to surgery. These two findings support those of previously published studies in an observational study of abdominal hysterectomy [172] and a clinical trial of gynecological surgery [158]. Moreover, many observational studies conducted in the surgical setting [167, 170, 178-180] have reported an increase in Hb levels similar to my results. Likewise, a recent systematic review and meta-analysis of the RCTs in anemic patients with inflammatory bowel disease showed a significantly higher ability of IV iron to achieving a Hb rise with better tolerance when compared to oral iron [182].

In this study, the pre-surgery Hb increase as a reserve was not sufficient to counteract the inevitable intraoperative acute blood loss in open heart surgery. This finding means that early preoperative supplementation with IV iron sucrose does not seem to hasten early recovery from anemia postoperatively. This result is also consistent with those of previously published trials particularly when the total dose of IV iron received was only 600 mg or less [108, 129, 130]. It would appear that Hb levels started to fall immediately after surgery due to acute blood loss, which may suggest a need for a greater dose of IV iron to be injected within four-week period pre-surgery followed by extra-doses before surgery. In this study, it is most likely that this negative drift in the Hb concentration during the postoperative period and at the discharge time is related to the too early

administration of the IV iron in addition to the relatively smaller doses used. The mean of the total dose of IV iron in this study was 573 mg (range: 300-1000 mg) of IV iron sucrose. This dose is about half the current treatments doses used in cardiac surgery clinical trials [157]. In some of the non-cardiac surgical studies [155, 156, 158], a dose of 1000 mg was used. Moreover, in a clinical trial involving anemia correction for uterine bleeding, the investigator used up to 3000 mg of IV iron with some participants [192].

In my institution, the early patients of this case series receive a dose of 300 mg as a total dose. This was based on findings from an early clinical trial [129], which was in progress at that time. Over time, the dose was gradually increased till some patients were administered 1000 mg. Typically, a dose of 600 mg is considered a moderate dose to treat perioperative anemia [130]. The second observation was that the mean time between completion of the iron sucrose dose and surgery was longer (59 days) than the time frame reported in other observational studies [180, 191] and clinical trials [130, 155, 160] where the interval ranged between 2 and 4 weeks preoperatively to have the optimal erythropoietic effect at the time of surgery. It is therefore possible that the current study patients might have missed the usual peak of the Hb increase by the time they had their surgery based on the findings of previous reports [180, 191] and the recommendations of the recent international consensus [184]. In this case series, the delay in the surgery time after treatment is mainly due to the nature of any elective operation where the patient picks a time convenient to him/her and the family. Moreover, the scheduled surgery time might be postponed due to the cancellation of the elective surgery in order to operate on emergencies like urgent/emergent CABG, and heart/lung transplants. The latter is particularly common reasons for postponing elective surgery since the institution is a

unique foundation across Canada that does heart and lung transplant in addition to insertion of many ventricular assistance devices (VADs) and extracorporeal membrane oxygenation (ECMO).

In this case series, IV iron was given to non-anemic patients, particularly the female portion who account for two-thirds of the study population, with the aim of ensuring a sufficient reserve of iron that could counteract the occurrence of adverse equilibrium in the body iron level resulting inevitably from the acute intraoperative blood loss to avoid transfusion. This negative imbalance should be corrected in advance to optimize the Hb concentration by enhancing the erythropoiesis.

The total RBCs transfusion rate in this series was 29%. Although there was no comparison group in this study, this transfusion proportion is lower than a recent Canadian report on adult cardiac surgery [193]. In this report, the transfusion rate in isolated CABG surgery was between 36%-41%, in isolated aortic valve replacement (AVR) surgery was 45%, and in combined CABG with AVR was 65%. Unfortunately, I was not able to access the Society of Thoracic surgeon (STS) database to compare the study transfusion rate with their data. However, in a recent extensive analysis of 42,743 patients [194] who had different adult cardiac surgery procedures at 25 institutions from Australia, there was a broad range of 22% to 67% of patients receiving at least one RBC unit, and the finding in the current case series finding falls near the lower limit of this range. In clinical trials of cardiac surgery patients, the transfusion rate ranged between 20% [157] to 36% [129] in the placebo groups, whereas in the IV iron groups, the transfusion rate ranged between 20% when a 300 mg dose was given [129] to 13% when the 1000 mg dose of IV iron was received [157]. In the current study, it was plausible to

expect that the patients with low Hb or serum ferritin levels were highly likely to require perioperative transfusion. However, neither Hb nor serum ferritin levels were associated with a tendency of blood transfusion. Moreover, the hospital LOS was similar between transfused and non-transfused patients, although it is possible that the small sample size led to insufficient power to detect a difference.

This case series has some limitations. First, as a case series, it yields low-quality evidence due to lack of control group of patients, making this case series prone to bias, particularly selection bias, and causality cannot be inferred. Second, it is a single-center non-analytic study with a small sample size and thus may not have had adequate power to detect associations. In addition, there was no comparison group of patients not receiving IV iron, which limits the inferences that can be made about the effectiveness of the intervention. In addition, these findings may not be generalizable to other institutions. The smaller size of this series is due to the fact that only a few surgeons at my institution refer elective cardiac surgery patients to the blood conservation clinic to have IV iron injections. In addition, there were multiple interruptions of the iron sucrose supply in the hospital, which also contributed to the small study size over a six-year period. Third, although this study included different cardiac-surgery patients (adult congenital, CABG, valve surgery), I was not able to do subgroup analysis due to the small sample size of the study. Fourth, I investigated only one of the IV iron preparations (iron sucrose) whereas many IV iron preparations now are available in the market. This was because IV iron sucrose is the one available at the study center most of the time due to its low price and it has been in the market for an extended period with its known great safety. Lastly, I did not have access to post-hospital discharge follow-up data for Hb level and transfusion.

However, it is unlikely that these patients will experience further blood loss post-discharge, thus it seems reasonable to believe that their Hb level likely will increase over their convalescence. Despite these limitations, this case series provides the necessary justification for the development of a large-scale clinical trial on this research question, which is now in the planning stages. That trial will provide more definitive answers.

4.6. CONCLUSION

To date, there are only a few studies available to investigate the efficacy of IV iron sucrose to optimize Hb to treat perioperative anemia in patients undergoing adult cardiac surgery. This case series adds to the small body of literature in this clinical setting as a bloodless strategy to avoid allogeneic blood transfusion. Notwithstanding these study limitations, these findings provide preliminary evidence that adult patients undergoing cardiac surgery, particularly anemic patients, can benefit from preoperative intravenous iron injection with higher doses with timely referral to avoid transfusion. Large-scale clinical trial conduction is still recommended to investigate which iron preparation, the optimal dose, the appropriate time of administration is efficient to reduce transfusion.

CHAPTER V: GENERAL DISCUSSION

This thesis reports findings from two studies: first, a systematic review and meta-analysis of studies which provides evidence supporting the effectiveness of preoperative IV iron administration in those with preoperative anemia; and, secondly, a case series which provides preliminary evidence that patients benefit from high dose and timely administration of preoperative IV iron. Together, these two studies provide solid support for a large clinical trial to investigate optimal preparations, dosage, and timing of preoperative IV iron administration to reduce the need for transfusions.

The question of the best management of preoperative anemia in surgical patients is a very important one to address. In patients undergoing major surgery, preoperative anemia is very common. Globally, it is a very frequent disease. Although its prevalence is less in first world countries than developing and under-developed countries, it is still a common problem, and about one-third of cardiac surgery [195, 196] and non-cardiac major surgery [74, 81] patients in the industrialized world experience anemia preoperatively. Multiple studies reported an increased incidence of perioperative morbidity and mortality in anemic patients experiencing cardiac [197-202] and non-cardiac [73, 81, 203-205] major operations.

It is to be expected that significant perioperative blood loss will occur in most major surgeries, particularly in orthopedic and cardiac operations. In a major orthopedic procedure, the estimated blood loss is about one liter, which accounts for one-fifth of the total adult circulating human blood [58]. The combination of perioperative blood loss and anemia usually necessitates blood transfusion. However, allogeneic blood transfusion

(ABT) is not without risks. It has been associated with higher rates of morbidity and mortality [206-208]. Furthermore, ABT carries risks such as the transmission of blood-borne pathogens [209], and specific morbid complications are associated with ABT. These morbid conditions include reduced tumor recurrence-free survival [210], tumor recurrence [86, 211], myocardial events, neurological events [85], acute kidney injury [212], transfusion-related acute lung injury (TRALI) [82], increased graft occlusion after CABG surgery [83], suppressed immune function [87], and nosocomial infections [84]. Interestingly, women receive more blood transfusions than men as reported in a large study of 6530 patients undergoing elective orthopedic and cardiac surgery [213]. This higher transfusion rate might be related to the smaller circulating blood volume in females than males [68]. Despite the growing work in perioperative bloodless management strategies, perioperative transfusion rate still high and correction of perioperative anemia with ABT is not without a price. Consequently, there has been a paradigm shift toward bloodless therapeutic strategies for dealing with perioperative anemia to improve patients' outcomes and use health care resources efficiently.

Iron deficiency anemia (IDA) is a common form of the preoperative anemia. IDA afflicts people of all ages particularly women of the childbearing period and aging people [136]. Preoperative iron deficiency (ID) is initiated mainly due to negative iron disequilibrium in the body iron level and aggravated more by the unavoidable bleeding during and post-surgery. Consequently, in the immediate postoperative period, acute anemia likely develops unless those exhausted stores are replenished sufficiently to counteract the perioperative blood loss. Therefore, the target of the therapy in preoperative IDA is to offer sufficient iron to correct this imbalance, to increase Hb level

and to minimize the ABT. In addition, preoperative optimization of the Hb concentration enhances tissue oxygenation post-surgery to help in quick recovery. Also, this Hb optimization might help to counteract the incidence of the inevitable immediate postoperative anemia that exists in up to 90% of cases after major surgery, as shown in a systematic review [60]. As per the recent practice guidelines for perioperative blood management of the American Society of Anesthesiologists Task Force on Perioperative Blood Management [214] and a recent review [190], preoperative optimization of Hb concentration is an effective strategy to minimize such transfusion. Plausibly, one would expect that preoperative iron repletion would help bone marrow to intensify erythropoiesis producing healthy RBCs with a regular lifecycle. It has been reported that transfused RBCs have a shorter lifespan than normal RBCs due to rapid clearance from the circulation [215].

As discussed earlier in this thesis, oral iron therapy is not the ideal form of iron administration in cases of preoperative anemia. It has a slow response or even no response, particularly in patients with ongoing bleeding or chronic medical conditions [216]. Therefore, IV iron treatment is more efficacious than oral form because the treatment course is very short due to its superior bioavailability [140] and this can avoid unnecessary delay of surgery. Moreover, a recent pooled analysis of 2547 patients [217] showed more benefit of IV iron over oral iron to minimize perioperative ABT. Therefore, IV iron usage was selected to be studied through the meta-analysis and the case series study where IV iron was administered or initiated preoperatively to allow for sufficient time to enhance erythropoiesis. It has been shown in a clinical trial and observational studies that giving IV iron shortly (within the four-week period) before the surgery is efficacious in

increasing Hb levels [160], [167, 170, 178, 179]. Interestingly, there is also evidence that an IV iron injection immediately after surgery is effective in treating anemia in orthopedic [218], stomach [219], and postpartum hemorrhage [220] surgery. Those results suggest that giving the IV shortly before surgery would be more efficacious than having a more extended time lag between the iron administration and surgery, and this is what the case series showed. However, there is no consistency in the literature regarding the dose, and which IV iron preparation is used. However, there is some evidence that higher dosages are more effective. Several randomized controlled trials (RCT) [108, 129, 130, 159] that used a dose not greater than 600 mg of IV iron therapy have shown no benefit in increasing Hb levels or to reducing ABTs perioperatively. More recent RCTs have started to use higher doses in a single 1000-mg dose of ferric carboxymaltose in abdominal surgery [156] and hip fracture surgery [155]. Similar single doses of IV iron isomaltoside was used recently in a cardiac surgery trial [157], and other trials have used repeated doses of 100 mg [160] or 200 mg [158] of IV iron sucrose on an alternate-day basis, with a total dose exceeding more than1000 mg before gynecological surgery in menorrhagia patients to correct preoperative anemia. Based on the finding of those studies, it is concluded that higher dosages are more effective. With regarding the more efficacious IV iron preparation, a recent systematic review and Bayesian network meta-analysis in inflammatory bowel disease showed that ferric carboxymaltose was the most effective IV formulation, followed by iron sucrose and iron isomaltose to normalize the Hb [144]. For the safety purposes, ferric carboxymaltose showed to have similar tolerability as iron dextran but tended to be better tolerated than iron sucrose, and iron isomaltose [144].

After reviewing all published RCTs investigating the optimal dose and timing for IV iron injection to treat perioperative anemia, it seems reasonable to hypothesize that administration of a large dose (1000 -1500 mg) within 2-4 weeks preoperatively will be efficacious to optimize the Hb levels perioperatively. Of note, over the last five years, the investigators have tended to increase the therapeutic dose of IV iron in the RCTs to maximize the patients' perioperative Hb. Specifically, the total iron dosage used in the RCT published in 2012 was only 300-mg [129]; this increased to a dose of 1000 mg or more in the RCTs published in 2016 [155, 156, 183] to treat perioperative anemia. Consequently, the most recent international consensus statement on the treatment of IDA in surgical patients recommended a dose of 1000–1500 mg administered in two divided doses [184]. This would appear to be no harm in using such large dose since a 2000-mg dose of IV iron was used safely in a clinical trial to treat severe uterine bleeding [192]. In that trial, 197 out of 230 patients received 2000 mg of ferric carboxymaltose in two divided doses with one-week apart. Moreover, 28/230 of the participants in the same study received 3000 mg of ferric carboxymaltose in three intermittent doses separated by one-week duration. The results of this trial imply high safety profile of ferric carboxymaltose that was transfused rapidly over 15 minutes without a testing dose, which is more convenient for the patients. Unfortunately, most the recent literature of IV iron therapy in the surgical setting, including the trials involved in the current meta-analysis, did not study the incidence of hypophosphatemia, which is potentially a side effect associated with a high dosage of IV iron therapy. In addition to parathormone and vitamin D, there is a new class of phosphate-regulating factors called phosphatonins [221]. One of these factors is

fibroblast growth factor 23 (FGF23), which regulates the renal phosphate excretion [222]. Only some IV iron preparations were associated with hypophosphatemia [192, 223, 224]. However, the mechanism is not apparently known. The carbohydrate moiety that exists in some IV iron preparations may reduce the intracellular FGF23 degradation [225]. Moreover, a recent study showed ferric carboxymaltose is associated with a severe and prolonged status of hypophosphatemia than iron isomaltoside [226]. The occurrence of hypophosphatemia varies widely from 34% [224] to 70% [192] of the patients. Therefore, phosphate level should be monitored before initiation and after IV iron therapy.

Based on the above discussion, I can conclude my thesis by summarizing that although preoperative anemia is an ongoing problem, there are promising solutions. Moreover, the short answer to my thesis question, that is *Is preoperative injection of intravenous iron a safe and effective treatment to increase hemoglobin and minimize allogeneic blood transfusion?* would appear to be “yes”, although more work is needed for the definitive answer.

5.1. CONCLUSION

The first step in solving this problem is establishing the correct diagnosis and the reason for the ID. In most patients, the ID should be treated with IV iron supplementation therapy to correct anemia and to replenish iron body store that indicated by normal or high serum ferritin. It may be necessary to distinguish the underlying etiology of the anemia, to correct it properly, and to avoid recurrence of the deficiency. The therapeutic objective is stabilization of Hb levels as rapidly as possible by administration of IV Iron.

The data presented in my thesis suggest that administration of large doses of the current IV iron agents, which contain more IV iron per preparation in a four-week window before surgery would be more efficient, and safe as a potential strategy to treat preoperative anemia. Further full-scale trials are still recommended to investigate such large doses in the operational setting. I think the design of the ideal further trials should to be statistically powered to the proportion of the transfused participants rather than the hemoglobin level change. A higher dose of IV iron should be given as per the most recent international consensus statement above (1000–1500 mg administered in two divided doses). Moreover, the outcomes should include in addition to the transfusion rate, hemoglobin and ferritin level change, quality of life, and the cost-effectiveness of the treatment.

References

[1] Baltierra D, Harper T, Jones MP, Nau KC: Hematologic disorders: Anemia. ***FP Essent*. 2015,** 433**:11-15.**

[2] Moreno Chulilla JA, Romero Colas MS, Gutierrez Martin M: Classification of anemia for gastroenterologists. ***World J Gastroenterol*. 2009,** 15**(37):4627-4637.**

[3] Camaschella C: Iron-deficiency anemia. ***N Engl J Med*. 2015,** 372**(19):1832-1843.**

[4] McLean E, Cogswell M, Egli I, Wojdyla D, de Benoist B: Worldwide prevalence of anaemia, WHO vitamin and mineral nutrition information system, 1993-2005. ***Public Health Nutr*. 2009,** 12**(4):444-454.**

[5] Sankaran VG, Weiss MJ: Anemia: Progress in molecular mechanisms and therapies. ***Nat Med*. 2015,** 21**(3):221-230.**

[6] World Health Organization. Vitamin and mineral nutrition information system; Haemoglobin concentrations for the diagnosis of anaemia and assessment of severity. **Geneva: World Health Organization; 2011 [http://www.who.int/vmnis/indicators/haemoglobin/en/index.html].**

[7] Xiong W, Wang L, Yu F: Regulation of cellular iron metabolism and its implications in lung cancer progression. ***Med Oncol*. 2014,** 31**(7):28-014-0028-2. Epub 2014 May 27.**

[8] Kautz L, Jung G, Valore EV, Rivella S, Nemeth E, Ganz T: Identification of erythroferrone as an erythroid regulator of iron metabolism. ***Nat Genet*. 2014,** 46**(7):678-684.**

[9] Mathers C, Stevens G, Mascarenhas M: Global health risks: Mortality and burden of disease attributable to selected major risks. . **Department of Health Statistics and Informatics, World Health Organization, Geneva, Switzerland,: 2009.**

[10] Ganz T, Nemeth E: Iron metabolism: Interactions with normal and disordered erythropoiesis. ***Cold Spring Harb Perspect Med*. 2012,** 2**(5):a011668.**

[11] Pasricha SR, Drakesmith H, Black J, Hipgrave D, Biggs BA: Control of iron deficiency anemia in low- and middle-income countries. ***Blood*. 2013,** 121**(14):2607-2617.**

[12] Johnson-Wimbley TD, Graham DY: Diagnosis and management of iron deficiency anemia in the 21st century. ***Therap Adv Gastroenterol*. 2011,** 4**(3):177-184.**

[13] Kassebaum NJ, Jasrasaria R, Naghavi M, Wulf SK, Johns N, Lozano R, Regan M, Weatherall D, Chou DP, Eisele TP, Flaxman SR, Pullan RL, Brooker SJ, Murray CJ: A systematic analysis of global anemia burden from 1990 to 2010. ***Blood*. 2014,** 123**(5):615-624.**

[14] Miller JL: Iron deficiency anemia: A common and curable disease. ***Cold Spring Harb Perspect Med*. 2013,** 3**(7):10.1101/cshperspect.a011866.**

[15] Zhu A, Kaneshiro M, Kaunitz JD: Evaluation and treatment of iron deficiency anemia: A gastroenterological perspective. ***Dig Dis Sci*. 2010,** 55**(3):548-559.**

[16] Rockey DC: Occult gastrointestinal bleeding. ***N Engl J Med*. 1999,** 341**(1):38-46.**

[17] UNICEF/United Nations University/World Health Organization(WHO): Iron deficiency anaemia: Assessment, prevention and control. A guide for programme managers. **Geneva: WHO: 2001.**

[18] Abbaspour N, Hurrell R, Kelishadi R: Review on iron and its importance for human health. ***J Res Med Sci*. 2014,** 19**(2):164-174.**

[19] Hentze MW, Muckenthaler MU, Galy B, Camaschella C: Two to tango: Regulation of mammalian iron metabolism. ***Cell*. 2010,** 142**(1):24-38.**

[20] Aisen P, Enns C, Wessling-Resnick M: Chemistry and biology of eukaryotic iron metabolism. ***Int J Biochem Cell Biol*. 2001,** 33**(10):940-959.**

[21] Lieu PT, Heiskala M, Peterson PA, Yang Y: The roles of iron in health and disease. ***Mol Aspects Med*. 2001,** 22**(1-2):1-87.**

[22] de Back DZ, Kostova EB, van Kraaij M, van den Berg TK, van Bruggen R: Of macrophages and red blood cells; a complex love story. ***Front Physiol*. 2014,** 5**:9.**

[23] Gottlieb Y, Truman M, Cohen LA, Leichtmann-Bardoogo Y, Meyron-Holtz EG: Endoplasmic reticulum anchored heme-oxygenase 1 faces the cytosol. ***Haematologica*. 2012,** 97**(10):1489-1493.**

[24] Zhang AS, Enns CA: Iron homeostasis: Recently identified proteins provide insight into novel control mechanisms. ***J Biol Chem*. 2009,** 284**(2):711-715.**

[25] Chan DS, Lau R, Aune D, Vieira R, Greenwood DC, Kampman E, Norat T: Red and processed meat and colorectal cancer incidence: Meta-analysis of prospective studies. ***PLoS One*. 2011,** 6**(6):e20456.**

[26] Larsson SC, Wolk A: Meat consumption and risk of colorectal cancer: A meta-analysis of prospective studies. ***Int J Cancer*. 2006,** 119**(11):2657-2664.**

[27] Qiao L, Feng Y: Intakes of heme iron and zinc and colorectal cancer incidence: A meta-analysis of prospective studies. ***Cancer Causes Control*. 2013,** 24**(6):1175-1183.**

[28] Bastide NM, Pierre FH, Corpet DE: Heme iron from meat and risk of colorectal cancer: A meta-analysis and a review of the mechanisms involved. ***Cancer Prev Res (Phila)*. 2011,** 4**(2):177-184.**

[29] Pourmoghaddas A, Sanei H, Garakyaraghi M, Esteki-Ghashghaei F, Gharaati M: The relation between body iron store and ferritin, and coronary artery disease. ***ARYA Atheroscler*. 2014,** 10**(1):32-36.**

[30] Andrews NC: Disorders of iron metabolism. ***N Engl J Med*. 1999,** 341**(26):1986-1995.**

[31] Kohgo Y, Ikuta K, Ohtake T, Torimoto Y, Kato J: Body iron metabolism and pathophysiology of iron overload. ***Int J Hematol*. 2008,** 88**(1):7-15.**

[32] Jain S, Gautam V, Naseem S: Acute-phase proteins: As diagnostic tool. ***J Pharm Bioallied Sci*. 2011,** 3**(1):118-127.**

[33] Saito H, Hayashi H, Tomita A, Ohashi H, Maeda H, Naoe T: Increasing and decreasing phases of ferritin and hemosiderin iron determined by serum ferritin kinetics. ***Nagoya J Med Sci*. 2013,** 75**(3-4):213-223.**

[34] Hunt JR, Zito CA, Johnson LK: Body iron excretion by healthy men and women. ***Am J Clin Nutr*. 2009,** 89**(6):1792-1798.**

[35] Wish JB: Assessing iron status: Beyond serum ferritin and transferrin saturation. ***Clin J Am Soc Nephrol*. 2006,** 1 Suppl 1**:S4-8.**

[36] Waldvogel-Abramowski S, Waeber G, Gassner C, Buser A, Frey BM, Favrat B, Tissot JD: Physiology of iron metabolism. ***Transfus Med Hemother*. 2014,** 41**(3):213-221.**

[37] Rossi E: Hepcidin--the iron regulatory hormone. ***Clin Biochem Rev*. 2005,** 26**(3):47-49.**

[38] Cucuianu A, Patiu M, Trifa AP, Tomuleasa C, Dima D: Redistribution of iron towards deposits in erythroblastopenic anemia as a consequence of decreased erythroferrone production. ***Med Hypotheses*. 2014,** 83**(5):530-532.**

[39] Rishi G, Wallace DF, Subramaniam VN: Hepcidin: Regulation of the master iron regulator. ***Biosci Rep*. 2015,** 35**(3):10.1042/BSR20150014.**

[40] D'Angelo G: Role of hepcidin in the pathophysiology and diagnosis of anemia. ***Blood Res*. 2013,** 48**(1):10-15.**

[41] Jimenez K, Kulnigg-Dabsch S, Gasche C: Management of iron deficiency anemia. ***Gastroenterol Hepatol (N Y)*. 2015,** 11**(4):241-250.**

[42] Bermejo F, Garcia-Lopez S: A guide to diagnosis of iron deficiency and iron deficiency anemia in digestive diseases. ***World J Gastroenterol*. 2009,** 15**(37):4638-4643.**

[43] Andrews NC: Molecular control of iron metabolism. ***Best Pract Res Clin Haematol*. 2005,** 18**(2):159-169.**

[44] Drakesmith H, Prentice AM: Hepcidin and the iron-infection axis. ***Science*. 2012,** 338**(6108):768-772.**

[45] Anderson GJ, McLaren GD. ***Iron physiology and pathophysiology in humans*** **. New York: Springer Science and Business Media; 2012.**

[46] Balarajan Y, Ramakrishnan U, Ozaltin E, Shankar AH, Subramanian SV: Anaemia in low-income and middle-income countries. ***Lancet*. 2011,** 378**(9809):2123-2135.**

[47] Beddall A: Anaemias. ***Practitioner*. 1990,** 234**(1492):713-715.**

[48] Chalmers AW, Shammo JM: Evaluation of a new tablet formulation of deferasirox to reduce chronic iron overload after long-term blood transfusions. ***Ther Clin Risk Manag*. 2016,** 12**:201-208.**

[49] Kujovich JL: Evaluation of anemia. ***Obstet Gynecol Clin North Am*. 2016,** 43**(2):247-264.**

[50] Barve S, Patel D, Shiromani KK, Jawarkar A: Role of RBC count and RBC indices in diagnosing and differentiating anemias caused due to various clinical situations in a tertiary care hospital in vadodara, gujarat. ***J of Evidence Based Med & Hlthcare*. 2015,** 2**(45):8146-8147, 8148.**

[51] Sharma S, Pujani M, Pahuja S, Chandra J, Rath B, Labhchand: Critical evaluation of peripheral smear in cases of anemia with high mean corpuscular hemoglobin concentration in children: A series of four cases. ***Indian J Pathol Microbiol*. 2010,** 53**(4):820-823.**

[52] Goddard AF, James MW, McIntyre AS, Scott BB, British Society of Gastroenterology: Guidelines for the management of iron deficiency anaemia. ***Gut*. 2011,** 60**(10):1309-1316.**

[53] Clark SF: Iron deficiency anemia: Diagnosis and management. ***Curr Opin Gastroenterol*. 2009,** 25**(2):122-128.**

[54] Guyatt GH, Oxman AD, Ali M, Willan A, McIlroy W, Patterson C: Laboratory diagnosis of iron-deficiency anemia: An overview. ***J Gen Intern Med*. 1992,** 7**(2):145-153.**

[55] Shibusa K, Hatayama M, Toki Y, Yamamoto M, Ito S, Shindo M, Fujiya M, Niizeki N, Tomoda Y, Kawai Y, Addo L, Ikuta K: Evaluation of basic performance of "point strip ferritin-3000" for simple and rapid quantification of serum ferritin. ***Rinsho Byori*. 2015,** 63**(12):1371-1376.**

[56] Knovich MA, Storey JA, Coffman LG, Torti SV, Torti FM: Ferritin for the clinician. ***Blood Rev*. 2009,** 23**(3):95-104.**

[57] Nissenson AR, Goodnough LT, Dubois RW: Anemia: Not just an innocent bystander? ***Arch Intern Med*. 2003,** 163**(12):1400-1404.**

[58] Kansagra AJ, Stefan MS: Preoperative anemia: Evaluation and treatment. ***Anesthesiol Clin*. 2016,** 34**(1):127-141.**

[59] Clevenger B, Richards T: Pre-operative anaemia. ***Anaesthesia*. 2015,** 70 Suppl 1**:20-8, e6-8.**

[60] Shander A, Knight K, Thurer R, Adamson J, Spence R: Prevalence and outcomes of anemia in surgery: A systematic review of the literature. ***Am J Med*. 2004,** 116**(7 SUPPL. 1):58-69.**

[61] Leichtle SW, Mouawad NJ, Lampman R, Singal B, Cleary RK: Does preoperative anemia adversely affect colon and rectal surgery outcomes? ***J Am Coll Surg*. 2011,** 212**(2):187-194.**

[62] Williams ML, He X, Rankin JS, Slaughter MS, Gammie JS: Preoperative hematocrit is a powerful predictor of adverse outcomes in coronary artery bypass graft surgery: A report from the society of thoracic surgeons adult cardiac surgery database. ***Ann Thorac Surg*. 2013,** 96**(5):1628-34; discussion 1634.**

[63] Deepak B, Balaji A, Pramod A, Sujit K, Savani F, Bapu K, Manish P, Yogesh B, Shreedhar J, Antony G: The prevalence and impact of preoperative anemia in patients undergoing cardiac surgery for rheumatic heart disease. ***J Cardiothorac Vasc Anesth*. 2016,** 30**(4):896-900.**

[64] Sabatine MS, Morrow DA, Giugliano RP, Burton PB, Murphy SA, McCabe CH, Gibson CM, Braunwald E: Association of hemoglobin levels with clinical outcomes in acute coronary syndromes. ***Circulation*. 2005,** 111**(16):2042-2049.**

[65] Reinecke H, Trey T, Wellmann J, Heidrich J, Fobker M, Wichter T, Walter M, Breithardt G, Schaefer RM: Haemoglobin-related mortality in patients undergoing percutaneous coronary interventions. ***Eur Heart J*. 2003,** 24**(23):2142-2150.**

[66] Shirzad M, Karimi A, Dowlatshahi S, et. al: Preoperative anemia associated in-hospital mortality and morbidity in isolated coronary artery bypass graft surgery ***CEJMed*. 2009,** 5**(3):308-314.**

[67] Goodnough LT, Maniatis A, Earnshaw P, Benoni G, Beris P, Bisbe E, Fergusson DA, Gombotz H, Habler O, Monk TG, Ozier Y, Slappendel R, Szpalski M: Detection, evaluation, and management of preoperative anaemia in the elective orthopaedic surgical patient: NATA guidelines. ***Br J Anaesth*. 2011,** 106**(1):13-22.**

[68] Munoz M, Gomez-Ramirez S, Kozek-Langeneker S, Shander A, Richards T, Pavia J, Kehlet H, Acheson AG, Evans C, Raobaikady R, Javidroozi M, Auerbach M: 'Fit to fly': Overcoming barriers to preoperative haemoglobin optimization in surgical patients. ***Br J Anaesth*. 2015,** 115**(1):15-24.**

[69] Gombotz H: Patient blood management: A patient-orientated approach to blood replacement with the goal of reducing anemia, blood loss and the need for blood transfusion in elective surgery. ***Transfus Med Hemother*. 2012,** 39**(2):67-72.**

[70] Hare GM, Baker JE, Pavenski K: Assessment and treatment of preoperative anemia: Continuing professional development. ***Canadian Journal of Anesthesia/Journal canadien d'anesthésie*. 2011,** 58**(6):569-581.**

[71] Munoz M, Gomez-Ramirez S, Campos A, Ruiz J, Liumbruno GM: Pre-operative anaemia: Prevalence, consequences and approaches to management. ***Blood Transfus*. 2015,** 13**(3):370-379.**

[72] Auerbach M: Intravenous iron in the perioperative setting. ***Am J Hematol*. 2014,** 89**(9):933.**

[73] Wu WC, Schifftner TL, Henderson WG, Eaton CB, Poses RM, Uttley G, Sharma SC, Vezeridis M, Khuri SF, Friedmann PD: Preoperative hematocrit levels and postoperative outcomes in older patients undergoing noncardiac surgery. ***JAMA*. 2007,** 297**(22):2481-2488.**

[74] Baron DM, Hochrieser H, Posch M, Metnitz B, Rhodes A, Moreno RP, Pearse RM, Metnitz P, European Surgical Outcomes Study (EuSOS) group for Trials Groups of European Society of Intensive Care Medicine, European Society of Anaesthesiology: Preoperative anaemia is associated with poor clinical outcome in non-cardiac surgery patients. ***Br J Anaesth*. 2014,** 113**(3):416-423.**

[75] Richards T, Musallam KM, Nassif J, Ghazeeri G, Seoud M, Gurusamy KS, Jamali FR: Impact of preoperative anaemia and blood transfusion on postoperative outcomes in gynaecological surgery. ***PLoS One*. 2015,** 10**(7):e0130861.**

[76] Boening A, Boedeker RH, Scheibelhut C, Rietzschel J, Roth P, Schonburg M: Anemia before coronary artery bypass surgery as additional risk factor increases the perioperative risk. ***Ann Thorac Surg*. 2011,** 92**(3):805-810.**

[77] Miceli A, Romeo F, Glauber M, de Siena PM, Caputo M, Angelini GD: Preoperative anemia increases mortality and postoperative morbidity after cardiac surgery. ***J Cardiothorac Surg*. 2014,** 9**:137-8090-9-137.**

[78] Jans O, Jorgensen C, Kehlet H, Johansson PI, Lundbeck Foundation Centre for Fast-track Hip and Knee Replacement Collaborative Group: Role of preoperative anemia for risk of transfusion and postoperative morbidity in fast-track hip and knee arthroplasty. ***Transfusion*. 2014,** 54**(3):717-726.**

[79] Tohme S, Varley PR, Landsittel DP, Chidi AP, Tsung A: Preoperative anemia and postoperative outcomes after hepatectomy. ***HPB (Oxford)*. 2016,** 18**(3):255-261.**

[80] Ferraris VA, Davenport DL, Saha SP, Austin PC, Zwischenberger JB: Surgical outcomes and transfusion of minimal amounts of blood in the operating room. ***Arch Surg*. 2012,** 147**(1):49-55.**

[81] Musallam K, Tamim H, Richards T, Spahn DR, Rosendaal FR, Habbal A, Khreiss M, Dahdaleh FS, Khavandi K, Sfeir PM, Soweid A, Hoballah JJ, Taher AT, Jamali FR: Preoperative anaemia and postoperative outcomes in non-cardiac surgery: A retrospective cohort study. ***Lancet*. 2011,** 378**(9800):1396-1407.**

[82] Bux J: Transfusion-related acute lung injury (TRALI): A serious adverse event of blood transfusion. ***Vox Sang*. 2005,** 89**(1):1-10.**

[83] Engoren M, Schwann TA, Jewell E, Neill S, Benedict P, Likosky DS, Habib RH: Is transfusion associated with graft occlusion after cardiac operations? ***Ann Thorac Surg*. 2015,** 99**(2):502-508.**

[84] Chang H, Hall GA, Geerts WH, Greenwood C, McLeod RS, Sher GD: Allogeneic red blood cell transfusion is an independent risk factor for the development of postoperative bacterial infection. ***Vox Sang*. 2000,** 78**(1):13-18.**

[85] Murphy GJ: Does blood transfusion harm cardiac surgery patients? ***BMC Med*. 2009,** 7**:38-7015-7-38.**

[86] Amato AC, Pescatori M: Effect of perioperative blood transfusions on recurrence of colorectal cancer: Meta-analysis stratified on risk factors. ***Dis Colon Rectum*. 1998,** 41**(5):570-585.**

[87] Brand A: Immunological aspects of blood transfusions. ***Blood Rev*. 2000,** 14**(3):130-144.**

[88] Geissler RG, Rotering H, Buddendick H, Franz D, Bunzemeier H, Roeder N, Kwiecien R, Sibrowski W, Scheld HH, Martens S, Schlenke P: Utilisation of blood components in cardiac surgery: A single-centre retrospective analysis with regard to diagnosis-related procedures. ***Transfus Med Hemother*. 2015,** 42**(2):75-82.**

[89] Koch CG: Tolerating anemia: Taking aim at the right target before pulling the transfusion trigger. ***Transfusion*. 2014,** 54**(10 Pt 2):2595-2597.**

[90] Cardone D, Klein AA: Perioperative blood conservation. ***Eur J Anaesthesiol*. 2009,** 26**(9):722-729.**

[91] Pattakos G, Koch CG, Brizzio ME, Batizy LH, Sabik JF,3rd, Blackstone EH, Lauer MS: Outcome of patients who refuse transfusion after cardiac surgery: A natural experiment with severe blood conservation. ***Arch Intern Med*. 2012,** 172**(15):1154-1160.**

[92] Rohde JM, Dimcheff DE, Blumberg N, Saint S, Langa KM, Kuhn L, Hickner A, Rogers MA: Health care-associated infection after red blood cell transfusion: A systematic review and meta-analysis. ***JAMA*. 2014,** 311**(13):1317-1326.**

[93] Munoz M, Garcia-Erce JA, Leal-Noval SR: Perioperative transfusion in anaemic patients undergoing coronary artery bypass. ***Lancet*. 2002,** 360**(9343):1427; author reply 1427-8.**

[94] Munoz M, Leal-Noval R, Garcia-Erce JA: Intravenous iron in cardiac surgery. ***Semin Hematol*. 2006,** 43**(SUPPL. 6):S39-S42.**

[95] Munoz M, Gomez-Ramirez S, Martin-Montanez E, Auerbach M: Perioperative anemia management in colorectal cancer patients: A pragmatic approach. ***World J Gastroenterol*. 2014,** 20**(8):1972-1985.**

[96] Bhandal N, Russell R: Intravenous versus oral iron therapy for postpartum anaemia. ***BJOG*. 2006,** 113**(11):1248-1252.**

[97] Shander A, Spence RK, Auerbach M: Can intravenous iron therapy meet the unmet needs created by the new restrictions on erythropoietic stimulating agents? ***Transfusion*. 2010,** 50**(3):719-732.**

[98] Paone G, Likosky DS, Brewer R, Theurer PF, Bell GF, Cogan CM, Prager RL, Membership of the Michigan Society of Thoracic and Cardiovascular Surgeons: Transfusion of 1 and 2 units of red blood cells is associated with increased morbidity and mortality. ***Ann Thorac Surg*****. 2014,** 97**(1):87-93; discussion 93-4.**

[99] Hopewell S, Omar O, Hyde C, Yu LM, Doree C, Murphy MF: A systematic review of the effect of red blood cell transfusion on mortality: Evidence from large-scale observational studies published between 2006 and 2010. ***BMJ Open*****. 2013,** 3**(5):10.1136/bmjopen-2012-002154.**

[100] Vamvakas EC, Carven JH: Allogeneic blood transfusion, hospital charges, and length of hospitalization: A study of 487 consecutive patients undergoing colorectal cancer resection. ***Arch Pathol Lab Med*****. 1998,** 122**(2):145-151.**

[101] Shander A, Hofmann A, Ozawa S, Theusinger OM, Gombotz H, Spahn DR: Activity-based costs of blood transfusions in surgical patients at four hospitals. ***Transfusion*****. 2010,** 50**(4):753-765.**

[102] Amin M, Fergusson D, Aziz A, Wilson K, Coyle D, Hebert P: The cost of allogeneic red blood cells--a systematic review. ***Transfus Med*****. 2003,** 13**(5):275-285.**

[103] Goodnough LT, Shander A: Patient blood management. ***Anesthesiology*****. 2012,** 116**(6):1367-1376.**

[104] Murphy MF, Stanworth SJ, Yazer M: Transfusion practice and safety: Current status and possibilities for improvement. ***Vox Sang*****. 2011,** 100**(1):46-59.**

[105] Leal-Noval SR, Rincon-Ferrari MD, Garcia-Curiel A, Herruzo-Aviles A, Camacho-Larana P, Garnacho-Montero J, Amaya-Villar R: Transfusion of blood components and postoperative infection in patients undergoing cardiac surgery. ***Chest*****. 2001,** 119**(5):1461-1468.**

[106] Reddy SM, Talwar S, Velayoudam D, Gharde P, Mallick V, Jha RK, Kumar L, Arkalgud SK: Multi-modality blood conservation strategy in open-heart surgery: An audit. ***Interact Cardiovasc Thorac Surg*****. 2009,** 9**(3):480-482.**

[107] Qian F, Osler TM, Eaton MP, Dick AW, Hohmann SF, Lustik SJ, Diachun CA, Pasternak R, Wissler RN, Glance LG: Variation of blood transfusion in patients undergoing major noncardiac surgery. ***Ann Surg*****. 2013,** 257**(2):266-278.**

[108] Serrano-Trenas JA, Ugalde PF, Cabello LM, Chofles LC, Lazaro PS, Benitez PC: Role of perioperative intravenous iron therapy in elderly hip fracture patients: A single-center randomized controlled trial. ***Transfusion*****. 2011,** 51**(1):97-104.**

[109] Goodnough LT, Nemeth E., Ganz T.: Detection, evaluation, and management of iron-restricted erythropoiesis. ***Blood*. 2010,** Dec 2;116**(23):4754-61.**

[110] KDOQI, National Kidney Foundation: II. clinical practice guidelines and clinical practice recommendations for anemia in chronic kidney disease in adults. ***Am J Kidney Dis*. 2006,** 47**(5 Suppl 3):S16-85.**

[111] Hofmann A, Farmer S, Towler SC: Strategies to preempt and reduce the use of blood products: An australian perspective. ***Curr Opin Anaesthesiol*. 2012,** 25**(1):66-73.**

[112] Beris P, Muñoz M, García-Erce JA, Thomas D, Maniatis A, Van Der Linden P: Perioperative anaemia management: Consensus statement on the role of intravenous iron. ***Br J Anaesth*. 2008,** 100**(5):599-604.**

[113] Kozek-Langenecker SA, Afshari A, Albaladejo P, Santullano CA, De Robertis E, Filipescu DC, Fries D, Gorlinger K, Haas T, Imberger G, Jacob M, Lance M, Llau J, Mallett S, Meier J, Rahe-Meyer N, Samama CM, Smith A, Solomon C, Van der Linden P, Wikkelso AJ, Wouters P, Wyffels P: Management of severe perioperative bleeding: Guidelines from the european society of anaesthesiology. ***Eur J Anaesthesiol*. 2013,** 30**(6):270-382.**

[114] Leal-Noval SR, Munoz M, Asuero M, Contreras E, Garcia-Erce JA, Llau JV, Moral V, Paramo JA, Quintana M, Spanish Expert Panel on Alternatives to Allogeneic Blood Transfusion: Spanish consensus statement on alternatives to allogeneic blood transfusion: The 2013 update of the "seville document". ***Blood Transfus*. 2013,** 11**(4):585-610.**

[115] Gurusamy KS, Nagendran M, Broadhurst JF, Anker SD, Richards T: Iron therapy in anaemic adults without chronic kidney disease. ***Cochrane Database Syst Rev*. 2014,** 12**:CD010640.**

[116] Froessler B, Tufanaru C, Cyna A, Pearson A: "Preoperative anemia management with intravenous iron: A systematic review.". ***JBI Library of Systematic Reviews and Implementation Reports*. 2013,** 11**(10):157-189.**

[117] Hallet J, Hanif A, Callum J, Pronina I, Wallace D, Yohanathan L, McLeod R, Coburn N: The impact of perioperative iron on the use of red blood cell transfusions in gastrointestinal surgery: A systematic review and meta-analysis. ***Transfus Med Rev*. 2014,** 28**(4):205-211.**

[118] Hogan M, Klein AA, Richards T: The impact of anaemia and intravenous iron replacement therapy on outcomes in cardiac surgery. ***Eur J Cardiothorac Surg*. 2015,** 47**(2):218-226.**

[119] Huedo-Medina TB, Sanchez-Meca J, Marin-Martinez F, Botella J: Assessing heterogeneity in meta-analysis: Q statistic or I2 index? ***Psychol Methods*****. 2006,** 11**(2):193.**

[120] Sun X, Ioannidis JP, Agoritsas T, Alba AC, Guyatt G: How to use a subgroup analysis: Users' guide to the medical literature. ***JAMA*****. 2014,** 311**(4):405-411.**

[121] The Nordic Cochrane Centre, The Cochrane Collaboration.: RevMan 5.3 beta | Informatics & Knowledge Management Department. **5.3.3. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration; 2014.**

[122] Song F, Khan KS, Dinnes J, Sutton AJ: Asymmetric funnel plots and publication bias in meta-analyses of diagnostic accuracy. ***Int J Epidemiol*****. 2002,** 31**(1):88-95.**

[123] Guyatt G, Oxman AD, Akl EA, Kunz R, Vist G, Brozek J, Norris S, Falck-Ytter Y, Glasziou P, DeBeer H, Jaeschke R, Rind D, Meerpohl J, Dahm P, Schunemann HJ: GRADE guidelines: 1. introduction-GRADE evidence profiles and summary of findings tables. ***J Clin Epidemiol*****. 2011,** 64**(4):383-394.**

[124] Perel P, Ker K, Morales Uribe CH, Roberts I: Tranexamic acid for reducing mortality in emergency and urgent surgery. ***Cochrane Database Syst Rev*****. 2013,** 1**:CD010245.**

[125] Henry DA, Carless PA, Moxey AJ, O'Connell D, Stokes BJ, Fergusson DA, Ker K: Anti-fibrinolytic use for minimising perioperative allogeneic blood transfusion. ***Cochrane Database Syst Rev*****. 2011,** (3):CD001886. doi**(3):CD001886.**

[126] Zufferey PJ, Miquet M, Quenet S, Martin P, Adam P, Albaladejo P, Mismetti P, Molliex S, tranexamic acid in hip-fracture surgery (THIF) study: Tranexamic acid in hip fracture surgery: A randomized controlled trial. ***Br J Anaesth*****. 2010,** 104**(1):23-30.**

[127] Glapsy J: Chapter 3: Recombinant human erythropoietin (rhEPO) in clinical oncology. In: **Thrombosis during therapy with erythropoiesis stimulating agents in cancer. 2008:745-757.**

[128] Kautz L, Nemeth E: Molecular liaisons between erythropoiesis and iron metabolism. ***Blood*****. 2014,** 124**(4):479-482.**

[129] GarridoMartin P, NassarMansur MI, de la LlanaDucros R, VirgosAller TM, Rodriguez Fortunez PM, AvalosPinto R, JimenezSosa A, MartinezSanz R: The effect of intravenous and oral iron administration on perioperative anaemia and transfusion requirements in patients undergoing elective cardiac surgery: A randomized clinical trial. ***Interactive cardiovascular and thoracic surgery*****. 2012,** 15**(6):1013-1018.**

[130] Edwards T, Noble E, Durran A, Mellor N, Hosie K: Randomized clinical trial of preoperative intravenous iron sucrose to reduce blood transfusion in anaemic patients after colorectal cancer surgery. ***Br J Surg*****. 2009,** 96**(10):1122-1128.**

[131] Kulnigg S, Stoinov S, Simanenkov V, Dudar LV, Karnafel W, Garcia LC, Sambuelli AM, D'Haens G, Gasche C: A novel intravenous iron formulation for treatment of anemia in inflammatory bowel disease: The ferric carboxymaltose (FERINJECT) randomized controlled trial. ***Am J Gastroenterol*****. 2008,** 103**(5):1182-1192.**

[132] Macdougall IC: Strategies for iron supplementation: Oral versus intravenous. ***Kidney Int Suppl*****. 1999,** 69**:S61-6.**

[133] Gupta A: Pathogenesis of anaphylactoid reactions to intravenous iron. ***Am J Kidney Dis*****. 2000,** 35**(2):360-361.**

[134] Kosch M, Bahner U, Bettger H, Matzkies F, Teschner M, Schaefer RM: A randomized, controlled parallel-group trial on efficacy and safety of iron sucrose (venofer) vs iron gluconate (ferrlecit) in haemodialysis patients treated with rHuEpo. ***Nephrol Dial Transplant*****. 2001,** 16**(6):1239-1244.**

[135] Guralnik JM, Eisenstaedt RS, Ferrucci L, Klein HG, Woodman RC: Prevalence of anemia in persons 65 years and older in the united states: Evidence for a high rate of unexplained anemia. ***Blood*****. 2004,** 104**(8):2263-2268.**

[136] Pasricha SR, Flecknoe-Brown SC, Allen KJ, Gibson PR, McMahon LP, Olynyk JK, Roger SD, Savoia HF, Tampi R, Thomson AR, Wood EM, Robinson KL: Diagnosis and management of iron deficiency anaemia: A clinical update. ***Med J Aust*****. 2010,** 193**(9):525-532.**

[137] Yanes Vidal GJ: Anemia in candidates for heart surgery. ***Rev Esp Anestesiol Reanim*****. 2015,** 62 Suppl 1**:69-75.**

[138] Bydon M, Abt NB, Macki M, Brem H, Huang J, Bydon A, Tamargo RJ: Preoperative anemia increases postoperative morbidity in elective cranial neurosurgery. ***Surg Neurol Int*****. 2014,** 5**:156-7806.143754. eCollection 2014.**

[139] George TJ, Beaty CA, Kilic A, Haggerty KA, Frank SM, Savage WJ, Whitman GJ: Hemoglobin drift after cardiac surgery. ***Ann Thorac Surg*****. 2012,** 94**(3):703-709.**

[140] Charytan C, Levin N, Al-Saloum M, Hafeez T, Gagnon S, Van Wyck DB: Efficacy and safety of iron sucrose for iron deficiency in patients with dialysis-associated anemia: North american clinical trial. ***Am J Kidney Dis*****. 2001,** 37**(2):300-307.**

[141] Beshara S, Lundqvist H, Sundin J, Lubberink M, Tolmachev V, Valind S, Antoni G, Langstrom B, Danielson BG: Pharmacokinetics and red cell utilization of iron(III) hydroxide-sucrose complex in anaemic patients: A study using positron emission tomography. ***Br J Haematol*. 1999,** 104**(2):296-302.**

[142] Bhavi SB, Jaju PB: Intravenous iron sucrose v/s oral ferrous fumarate for treatment of anemia in pregnancy. A randomized controlled trial. ***BMC Pregnancy Childbirth*. 2017,** 17**(1):137-017-1313-9.**

[143] Lebrun F, Klastersky J, Levacq D, Wissam Y, Paesmans M: Intravenous iron therapy for anemic cancer patients: A review of recently published clinical studies. ***Support Care Cancer*. 2017, .**

[144] Aksan A, Isik H, Radeke HH, Dignass A, Stein J: Systematic review with network meta-analysis: Comparative efficacy and tolerability of different intravenous iron formulations for the treatment of iron deficiency anaemia in patients with inflammatory bowel disease. ***Aliment Pharmacol Ther*. 2017,** 45**(10):1303-1318.**

[145] Moher D, Shamseer L, Clarke M, Ghersi D, Liberati A, Petticrew M, Shekelle P, Stewart LA, PRISMA-P Group: Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. ***Syst Rev*. 2015,** 4**:1-4053-4-1.**

[146] Higgins JP, Altman DG, Gotzsche PC, Juni P, Moher D, Oxman AD, Savovic J, Schulz KF, Weeks L, Sterne JA, Cochrane Bias Methods Group, Cochrane Statistical Methods Group: The cochrane collaboration's tool for assessing risk of bias in randomised trials. ***BMJ*. 2011,** 343**:d5928.**

[147] Thompson SG, Higgins JP: How should meta-regression analyses be undertaken and interpreted? ***Stat Med*. 2002,** 21**(11):1559-1573.**

[148] Follmann D, Elliott P, Suh I, Cutler J: Variance imputation for overviews of clinical trials with continuous response. ***J Clin Epidemiol*. 1992,** 45**(7):769-773.**

[149] Borenstein M, Hedges LV, Higgins JPT, Rothstein HR: Fixed-effect versus random-effect models. In: **Introduction to Meta-Analysis. First editionUnited Kingdom: John Wiley & Sons, Ltd. ISBN: 978-0-470-05724-7; 2009:61-85.**

[150] DerSimonian R, Laird N: Meta-analysis in clinical trials. ***Control Clin Trials*. 1986,** 7**(3):177-188.**

[151] Higgins J, Green S. ***Cochrane handbook for systematic reviews of interventions*** **Version 5.1.0 [updated march 2011]. version 5.1.0 ed. Higgins JPT GS, editor. Available from www.handbook.cochrane.org.: The Cochrane Collaboration; 2011.**

[152] MANTEL N, HAENSZEL W: Statistical aspects of the analysis of data from retrospective studies of disease. ***J Natl Cancer Inst*. 1959,** 22**(4):719-748.**

[153] Friedrich JO, Adhikari NK, Beyene J: Inclusion of zero total event trials in meta-analyses maintains analytic consistency and incorporates all available data. ***BMC Med Res Methodol*. 2007,** 7**:5.**

[154] Tobias A: Assessing the influence of a single study in the meta- analysis estimate. ***Stata Techn Bull*. 1999,** 8**:15-17.**

[155] Bernabeu-Wittel M, Romero M, Ollero-Baturone M, Aparicio R, Murcia-Zaragoza J, Rincon-Gomez M, Monte-Secades R, Melero-Bascones M, Rosso CM, Ruiz-Cantero A, PAHFRAC-01 Investigators: Ferric carboxymaltose with or without erythropoietin in anemic patients with hip fracture: A randomized clinical trial. ***Transfusion*. 2016,** 56**(9):2199-2211.**

[156] Froessler B., - PP, - WI, - HN, - SR, - ME: The important role for intravenous iron in perioperative patient blood management in major abdominal surgery: A randomized controlled trial. ***Ann Surg*. 2016,** 264**(1):41-46.**

[157] Johansson PI, Rasmussen AS, Thomsen LL: Intravenous iron isomaltoside 1000 (monofer(R)) reduces postoperative anaemia in preoperatively non-anaemic patients undergoing elective or subacute coronary artery bypass graft, valve replacement or a combination thereof: A randomized double-blind placebo-controlled clinical trial (the PROTECT trial). ***Vox Sang*. 2015,** 109**(3):257-266.**

[158] Kim YH, Chung HH, Kang SB, Kim SC, Kim YT: Safety and usefulness of intravenous iron sucrose in the management of preoperative anemia in patients with menorrhagia: A phase IV, open-label, prospective, randomized study. ***Acta Haematol*. 2009,** 121**(1):37-41.**

[159] Weisbach V, Skoda P, Rippel R, Lauer G, Glaser A, Zingsem J, Zimmermann R, Eckstein R: Oral or intravenous iron as an adjuvant to autologous blood donation in elective surgery: A randomized, controlled study. ***Transfusion*. 1999,** 39**(5):465-472.**

[160] Shah J, Vachhanai A, Mehta M, Kongnathi S: Safety and effectivness of intravenous iron sucrose versus oral iron: A study among preoperative anemic women with menorragia. ***National Journal of Community Medicine*│*Volume 7*│*Issue 1*│*Jan 2016*. 2016,** 7**(1):60-63.**

[161] Ware JE, Kosinski M, Gandek B, New England Medical Center Hospital. SF-36 health survey: Manual and interpretation guide. Boston, Mass.: The Health Institution, New England Medical Center Hospital; 2002.

[162] Ware JE,Jr, Sherbourne CD: The MOS 36-item short-form health survey (SF-36). I. conceptual framework and item selection. ***Med Care*****. 1992,** 30**(6):473-483.**

[163] Wright A, Hannon J, Hegedus EJ, Kavchak AE: Clinimetrics corner: A closer look at the minimal clinically important difference (MCID). ***J Man Manip Ther*****. 2012,** 20**(3):160-166.**

[164] Richards T, Clevenger B, Keidan J, Collier T, Klein AA, Anker SD, Kelly JD: PREVENTT: Preoperative intravenous iron to treat anaemia in major surgery: Study protocol for a randomised controlled trial. ***Trials*****. 2015,** 16**:254-015-0774-2.**

[165] Keeler BD, Simpson JA, Ng S, Tselepis C, Iqbal T, Brookes MJ, Acheson AG: The feasibility and clinical efficacy of intravenous iron administration for preoperative anaemia in patients with colorectal cancer. ***Colorectal Dis*****. 2014,** 16**(10):794-800.**

[166] Quinn EM, Meland E, McGinn S, Anderson JH: Correction of iron-deficiency anaemia in colorectal surgery reduces perioperative transfusion rates: A before and after study. ***Int J Surg*****. 2017,** 38**:1-8.**

[167] Calleja JL, Delgado S, del Val A, Hervas A, Larraona JL, Teran A, Cucala M, Mearin F, Colon Cancer Study Group: Ferric carboxymaltose reduces transfusions and hospital stay in patients with colon cancer and anemia. ***Int J Colorectal Dis*****. 2016,** 31**(3):543-551.**

[168] Laso-Morales M, Gomez R, Pontes G, Díaz EC., Munoz M: Intravenous versus oral iron for treating iron deficiency anaemia in colorectal cancer patients: A single-centre, observational cohort study

Transfusion Medicine**. 2016,** 26(Suppl. 1)**:53.**

[169] Blanco Rubio N, Llorens Eizaguerri M, Seral Garcia B, Burillo Fuertes P, Ranera Garcia M, Albareda Albareda J: Preoperative intravenous iron as a strategy for blood saving in surgery for hip fracture. ***Med Clin (Barc)*****. 2013,** 141**(9):371-375.**

[170] Bisbe E, Garcia-Erce JA, Diez-Lobo Al, Munoz M, Anaemia Working Group Espana: A multicentre comparative study on the efficacy of intravenous ferric carboxymaltose and iron sucrose for correcting preoperative anaemia in patients undergoing major elective surgery. ***Br J Anaesth*****. 2011,** 107**(3):477-478.**

[171] Diaz Espallardo C, Laso Morales MJ, Colilles Calvet C, Mora Lopez L, Roig Martinez I, Martinez Marin MT: The multidisciplinary approach is useful for optimising preoperative haemoglobin in colorectal cancer surgery. ***Cir Esp*****. 2011,** 89**(6):392-399.**

[172] Diez-Lobo A, Fisac-Mart´ın M, Bermejo-Aycar I, Munoz M: Preoperative intravenous iron administration corrects anemia and reduces transfusion requirement in women undergoing abdominal hysterectomy. . ***Transfus Altern Med*. 2007,** 9**(2):114-119.**

[173] Cuenca J, Garcia-Erce JA, Martinez AA, Solano VM, Molina J, Munoz M: Role of parenteral iron in the management of anaemia in the elderly patient undergoing displaced subcapital hip fracture repair: Preliminary data. ***Arch Orthop Trauma Surg*. 2005,** 125**(5):342-347.**

[174] Garcia Erce JA, Cuenca Espierrez J, Solano Bernad VM, Munoz Gomez M: [Erythropoietin as an alternative to allogenic transfusion in major orthopedic surgery]. ***Rev Esp Anestesiol Reanim*. 2004,** 51**(3):169-170.**

[175] IRONMAN Investigators, Litton E, Baker S, Erber WN, Farmer S, Ferrier J, French C, Gummer J, Hawkins D, Higgins A, Hofmann A, De Keulenaer B, McMorrow J, Olynyk JK, Richards T, Towler S, Trengove R, Webb S, Australian and New Zealand Intensive Care Society Clinical Trials Group: Intravenous iron or placebo for anaemia in intensive care: The IRONMAN multicentre randomized blinded trial : A randomized trial of IV iron in critical illness. ***Intensive Care Med*. 2016,** 42**(11):1715-1722.**

[176] Shah A, Roy NB, McKechnie S, Doree C, Fisher SA, Stanworth SJ: Iron supplementation to treat anaemia in adult critical care patients: A systematic review and meta-analysis. ***Crit Care*. 2016,** 20**(1):306.**

[177] Simpson J, Ng S, Brookes M, Acheson A: Single dose preoperative administration of intravenous iron corrects iron deficiency anaemia in colorectal cancer. ***J Blood Disord Transfus*. 2010,** 1**(Issue 1•1000101 doi: 10.4172/2155-9864.).**

[178] Munoz M. Garcia-Erce JA. Diez-Lobo Al. Campos A. Sebastianes C. Bisbe E. Anaemia Working Group Espana (AWGE): [Usefulness of the administration of intravenous iron sucrose for the correction of preoperative anemia in major surgery patients]. ***Med Clin (Barc)*. 2009,** 132**(8):303-306.**

[179] Garcia-Erce JA, Cuenca J, Munoz M, Izuel M, Martinez AA, Herrera A, Solano VM, Martinez F: Perioperative stimulation of erythropoiesis with intravenous iron and erythropoietin reduces transfusion requirements in patients with hip fracture. A prospective observational study. ***Vox Sang*. 2005,** 88**(4):235-243.**

[180] Theusinger OM, Leyvraz PF, Schanz U, Seifert B, Spahn DR: Treatment of iron deficiency anemia in orthopedic surgery with intravenous iron: Efficacy and limits: A prospective study. ***Anesthesiology 2007 Dec;107(6):923-7*. 2007,** 107**(6):923-7.**

[181] Rognoni C, Venturini S, Meregaglia M, Marmifero M, Tarricone R: Efficacy and safety of ferric carboxymaltose and other formulations in iron-deficient patients: A systematic review and network meta-analysis of randomised controlled trials. ***Clin Drug Investig*. 2016,** 36**(3):177-194.**

[182] Bonovas S, Fiorino G, Allocca M, Lytras T, Tsantes A, Peyrin-Biroulet L, Danese S: Intravenous versus oral iron for the treatment of anemia in inflammatory bowel disease: A systematic review and meta-analysis of randomized controlled trials. ***Medicine (Baltimore)*. 2016,** 95**(2):e2308.**

[183] Khalafallah AA, Yan C, Al-Badri R, Robinson E, Kirkby BE, Ingram E, Gray Z, Khelgi V, Robertson IK, Kirkby BP: Intravenous ferric carboxymaltose versus standard care in the management of postoperative anaemia: A prospective, open-label, randomised controlled trial. ***Lancet Haematol*. 2016,** 3**(9):e415-25.**

[184] Munoz M, Acheson AG, Auerbach M, Besser M, Habler O, Kehlet H, Liumbruno GM, Lasocki S, Meybohm P, Rao Baikady R, Richards T, Shander A, So-Osman C, Spahn DR, Klein AA: International consensus statement on the peri-operative management of anaemia and iron deficiency. ***Anaesthesia*. 2017,** 72**(2):233-247.**

[185] Torres S, Kuo YH, Morris K, Neibart R, Holtz JB, Davis JM: Intravenous iron following cardiac surgery does not increase the infection rate. ***Surg Infect (Larchmt)*. 2006,** 7**(4):361-366.**

[186] Auerbach M, Chaudhry M, Goldman H, Ballard H: Value of methylprednisolone in prevention of the arthralgia-myalgia syndrome associated with the total dose infusion of iron dextran: A double blind randomized trial. ***J Lab Clin Med*. 1998,** 131**(3):257-260.**

[187] Wysowski DK, Swartz L, Borders-Hemphill BV, Goulding MR, Dormitzer C: Use of parenteral iron products and serious anaphylactic-type reactions. ***Am J Hematol*. 2010,** 85**(9):650-654.**

[188] Rosenthal L, Schisterman E: Meta-analysis: Drawing conclusions when study results vary. ***Methods Mol Biol*. 2010,** 594**:427-434.**

[189] Shander A, Javidroozi M, Ozawa S, Hare GM: What is really dangerous: Anaemia or transfusion? ***Br J Anaesth*. 2011,** 107 Suppl 1**:i41-59.**

[190] Bisbe E, Basora M, Colomina MJ, Spanish Best Practice in Peri-operative Anaemia Optimisation Panel (see Appendix 1): Peri-operative treatment of anaemia in major orthopaedic surgery: A practical approach from spain. ***Blood Transfus*. 2017, :1-11.**

[191] Goodnough LT, Skikne B, Brugnara C: Erythropoietin, iron, and erythropoiesis. ***Blood*. 2000,** 96**(3):823-833.**

[192] Van Wyck DB, Mangione A, Morrison J, Hadley PE, Jehle JA, Goodnough LT: Large-dose intravenous ferric carboxymaltose injection for iron deficiency anemia in heavy uterine bleeding: A randomized, controlled trial. ***Transfusion*. 2009,** 49**(12):2719-2728.**

[193] Oakes G, Feindel C, Purdham D, Tu J, Wang J, Kingsbury K: Report on adult cardiac surgery in ontario. **Toronto, ON, Canada: The Cardiac Care Network of Ontario (CCN), in collaboration with the Institute for Clinical Evaluative Sciences (ICES); 2012.**

[194] McQuilten ZK, Andrianopoulos N, Wood EM, Cole-Sinclair MF, McNeil JJ, Cameron PA, Reid CM, Newcomb AE, Smith JA, Phillips LE: Transfusion practice varies widely in cardiac surgery: Results from a national registry. ***J Thorac Cardiovasc Surg*. 2014,** 147**(5):1684-1690.e1.**

[195] Klein AA, Collier TJ, Brar MS, Evans C, Hallward G, Fletcher SN, Richards T, Association of Cardiothoracic Anaesthetists (ACTA): The incidence and importance of anaemia in patients undergoing cardiac surgery in the UK - the first association of cardiothoracic anaesthetists national audit. ***Anaesthesia*. 2016,** 71**(6):627-635.**

[196] De Santo L, Romano G, Della Corte A, de Simone V, Grimaldi F, Cotrufo M, de Feo M: Preoperative anemia in patients undergoing coronary artery bypass grafting predicts acute kidney injury. ***J Thorac Cardiovasc Surg*. 2009,** 138**(4):965-970.**

[197] Zindrou D, Taylor KM, Bagger JP: Preoperative haemoglobin concentration and mortality rate after coronary artery bypass surgery. ***Lancet*. 2002,** 359**(9319):1747-1748.**

[198] Cladellas M, Bruguera J, Comin J, Vila J, de Jaime E, Marti J, Gomez M: Is pre-operative anaemia a risk marker for in-hospital mortality and morbidity after valve replacement? ***Eur Heart J*. 2006,** 27**(9):1093-1099.**

[199] Kulier A, Levin J, Moser R, Rumpold-Seitlinger G, Tudor IC, Snyder-Ramos SA, Moehnle P, Mangano DT: Impact of preoperative anemia on outcome in patients undergoing coronary artery bypass graft surgery. ***Circulation*. 2007,** 116**(5):471-479.**

[200] Karkouti K, Wijeysundera DN, Beattie WS, Reducing Bleeding in Cardiac Surgery (RBC) Investigators: Risk associated with preoperative anemia in cardiac surgery: A multicenter cohort study. ***Circulation*. 2008,** 117**(4):478-484.**

[201] van Straten AH, Hamad MA, van Zundert AJ, Martens EJ, Schonberger JP, de Wolf AM: Preoperative hemoglobin level as a predictor of survival after coronary

artery bypass grafting: A comparison with the matched general population. ***Circulation*. 2009,** 120**(2):118-125.**

[202] Ranucci M, Di Dedda U, Castelvecchio S, Menicanti L, Frigiola A, Pelissero G, Surgical and Clinical Outcome Research (SCORE) Group: Impact of preoperative anemia on outcome in adult cardiac surgery: A propensity-matched analysis. ***Ann Thorac Surg*. 2012,** 94**(4):1134-1141.**

[203] Beattie WS, Karkouti K, Wijeysundera DN, Tait G: Risk associated with preoperative anemia in noncardiac surgery: A single-center cohort study. ***Anesthesiology*. 2009,** 110**(3):574-581.**

[204] Gupta PK, Sundaram A, Mactaggart JN, Johanning JM, Gupta H, Fang X, Forse RA, Balters M, Longo GM, Sugimoto JT, Lynch TG, Pipinos II: Preoperative anemia is an independent predictor of postoperative mortality and adverse cardiac events in elderly patients undergoing elective vascular operations. ***Ann Surg*. 2013,** 258**(6):1096-1102.**

[205] Saager L, Turan A, Reynolds LF, Dalton JE, Mascha EJ, Kurz A: The association between preoperative anemia and 30-day mortality and morbidity in noncardiac surgical patients. ***Anesth Analg*. 2013,** 117**(4):909-915.**

[206] Murphy GJ, Reeves BC, Rogers CA, Rizvi SI, Culliford L, Angelini GD: Increased mortality, postoperative morbidity, and cost after red blood cell transfusion in patients having cardiac surgery. ***Circulation*. 2007,** 116**(22):2544-2552.**

[207] Shokoohi A, Stanworth S, Mistry D, Lamb S, Staves J, Murphy MF: The risks of red cell transfusion for hip fracture surgery in the elderly. ***Vox Sang*. 2012,** 103**(3):223-230.**

[208] Weber WP, Zwahlen M, Reck S, Misteli H, Rosenthal R, Buser AS, Kaufmann M, Oertli D, Widmer AF, Marti WR: The association of preoperative anemia and perioperative allogeneic blood transfusion with the risk of surgical site infection. ***Transfusion*. 2009,** 49**(9):1964-1970.**

[209] Dellinger EP, Anaya DA: Infectious and immunologic consequences of blood transfusion. ***Crit Care*. 2004,** 8 Suppl 2**:S18-23.**

[210] Cata JP, Lasala J, Pratt G, Feng L, Shah JB: Association between perioperative blood transfusions and clinical outcomes in patients undergoing bladder cancer surgery: A systematic review and meta-analysis study. ***J Blood Transfus*. 2016,** 2016**:9876394.**

[211] Wang YL, Jiang B, Yin FF, Shi HQ, Xu XD, Zheng SS, Wu S, Hou SC: Perioperative blood transfusion promotes worse outcomes of bladder cancer after

radical cystectomy: A systematic review and meta-analysis. ***PLoS One*. 2015,** 10**(6):e0130122.**

[212] Freeland K, Hamidian Jahromi A, Duvall LM, Mancini MC: Postoperative blood transfusion is an independent predictor of acute kidney injury in cardiac surgery patients. ***J Nephropathol*. 2015,** 4**(4):121-126.**

[213] Gombotz H, Schreier G, Neubauer S, Kastner P, Hofmann A: Gender disparities in red blood cell transfusion in elective surgery: A post hoc multicentre cohort study. ***BMJ Open*. 2016,** 6**(12):e012210-2016-012210.**

[214] American Society of Anesthesiologists Task Force on Perioperative Blood Management: Practice guidelines for perioperative blood management: An updated report by the american society of anesthesiologists task force on perioperative blood management*. ***Anesthesiology*. 2015,** 122**(2):241-275.**

[215] Kickler TS, Smith B, Bell W, Drew H, Baldwin M, Ness PM: Estimation of transfused red cell survival using an enzyme-linked antiglobulin test. ***Transfusion*. 1985,** 25**(5):401-405.**

[216] Munoz M, Garcia-Erce JA, Remacha AF: Disorders of iron metabolism. part II: Iron deficiency and iron overload. ***J Clin Pathol*. 2011,** 64**(4):287-296.**

[217] Munoz M, Gomez-Ramirez S, Cuenca J, Garcia-Erce JA, Iglesias-Aparicio D, Haman-Alcober S, Ariza D, Naveira E: Very-short-term perioperative intravenous iron administration and postoperative outcome in major orthopedic surgery: A pooled analysis of observational data from 2547 patients. ***Transfusion*. 2014,** 54**(2):289-299.**

[218] Bisbe E, Molto L, Arroyo R, Muniesa JM, Tejero M: Randomized trial comparing ferric carboxymaltose vs oral ferrous glycine sulphate for postoperative anaemia after total knee arthroplasty. ***Br J Anaesth*. 2014,** 113**(3):402-409.**

[219] Yoon HM, Kim Y-, Nam BH, Reim D, Eom BW, Park JY, Ryu KW: Intravenous iron supplementation may be superior to observation in acute isovolemic anemia after gastrectomy for cancer. ***World Journal of Gastroenterology*. 2014,** 20**(7):1852-1857.**

[220] Seid MH, Derman RJ, Baker JB, Banach W, Goldberg C, Rogers R: Ferric carboxymaltose injection in the treatment of postpartum iron deficiency anemia: A randomized controlled clinical trial. ***Am J Obstet Gynecol*. 2008,** 199**(4):435.e1-435.e7.**

[221] Berndt T, Kumar R: Phosphatonins and the regulation of phosphate homeostasis. ***Annu Rev Physiol*. 2007,** 69**:341-359.**

[222] Haussler MR, Whitfield GK, Kaneko I, Forster R, Saini R, Hsieh JC, Haussler CA, Jurutka PW: The role of vitamin D in the FGF23, klotho, and phosphate bone-kidney endocrine axis. ***Rev Endocr Metab Disord*. 2012,** 13**(1):57-69.**

[223] Tan SJ, Satake S, Smith ER, Toussaint ND, Hewitson TD, Holt SG: Parenteral iron polymaltose changes i:C-terminal FGF23 ratios in iron deficiency, but not in dialysis patients. ***Eur J Clin Nutr*. 2017,** 71**(2):180-184.**

[224] Hardy S, Vandemergel X: Intravenous iron administration and hypophosphatemia in clinical practice. ***Int J Rheumatol*. 2015,** 2015**:468675.**

[225] Wolf M, Koch TA, Bregman DB: Effects of iron deficiency anemia and its treatment on fibroblast growth factor 23 and phosphate homeostasis in women. ***J Bone Miner Res*. 2013,** 28**(8):1793-1803.**

[226] Schaefer B, Wurtinger P, Finkenstedt A, Braithwaite V, Viveiros A, Effenberger M, Sulzbacher I, Moschen A, Griesmacher A, Tilg H, Vogel W, Zoller H: Choice of high-dose intravenous iron preparation determines hypophosphatemia risk. ***PLoS One*. 2016,** 11**(12):e0167146.**

APPENDICES

6.1. APPENDIX 1: SAMPLE SEARCH STRATEGY

MEDLINE through OVID search strategy

Database: Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) <1946 to Present> December 15, 2016

1. Iron/
2. exp Iron Compounds/
3. (iron or dextran or venofer or ferric or ferrous or ferrlecit).mp. [mp =title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier]
4. 1 or 2 or 3
5. exp Anemia/
6. (anemi* or anaemi*).mp. [mp =title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier]
7. 5 or 6
8. 4 and 7
9. exp perioperative care/ or exp perioperative period/
10. exp Specialties, Surgical/
11. exp Surgical Procedures, Operative/
12. (preoperat* or postoperat* or perioperat* or operati* or surg* or presurg* or postsurg* or perisurg*).mp. [mp =title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier]
13. 9 or 10 or 11 or 12
14. 8 and 13

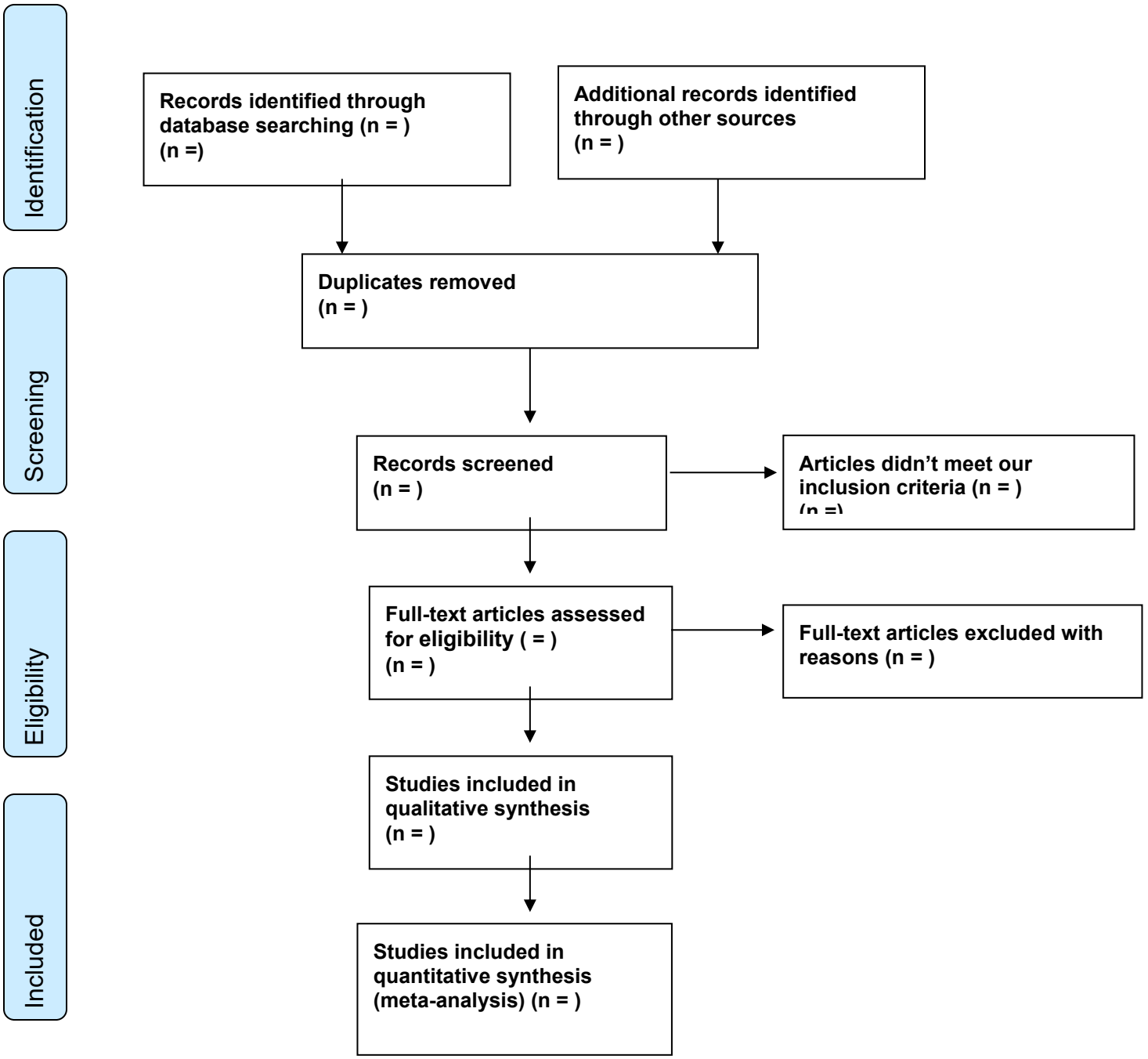
15. randomized controlled trial.pt.
16. clinical trial.pt.
17. randomi?ed.ti,ab.
18. placebo.ti,ab.
19. dt.fs.
20. randomly.ti,ab.
21. trial.ti,ab.
22. groups.ti,ab.
23. or/15-22
24. animals/
25. humans/
26. 24 not (24 and 25)
27. 23 not 26
28. 14 and 27

6.2. APPENDIX 2: DEFINITIONS

- Major surgery is defined as any aggressive operating technique in which an organ was excised, a wide resection was achieved, organs are removed, a body cavity was entered, or normal body anatomy was distorted.
- Post-operative nosocomial infection defined as having temperature >38°C in the last 24 hours with signs indicating infection and/or receiving antimicrobials beyond those used for routine perioperative prophylaxis.
- Transfusion-related acute lung injury (TRALI) syndrome, defined as a condition of acute respirational distress, which follows a recent allogeneic blood transfusion without having any pre-existing lung damage.
- Neurologic complications, defined as any focal neurological insufficiency in the form of new stroke, seizure, or transient ischemic attack. It could be associated with/without decreased level of consciousness.
- Acute kidney injury, defined as presence of oliguria (urine output less than 500 ml/24 hours) and/or an increase in serum creatinine level greater than 25% or 44.2 µmol/L from a stable pre-operative baseline level.
- Any reported reaction or side outcome from receiving allogeneic blood transfusion. These may involve but are not limited to: hemolysis of transfused red cells; fever; iron overload; alloimmunization; formation of antibodies against any of the blood elements; post-transfusion purpura; graft vs. host disease; immunomodulation; or infection.
- Any reported adverse reaction, defined as any damaging influence that is hypothetically related to the use of IV iron injection that necessitates a therapy, and/or withdrawal of the IV iron, or alteration of the dosage regimen.
- An unexpected adverse reaction is any adverse reaction to IV iron with different severity or nature not reported in the information about IV iron injection either in marketing summary of product, previous literature, or in the investigator's trial protocol.

- Serious adverse events (SAEs), is defined as any anticipated or unpredicted adverse event that will be described as a harmful reaction potentially caused by IV iron injection necessitating extension of the current hospital stay or a new hospital admission, causing significant disability, producing congenital abnormality, or mortality.

6.3. APPENDIX 3: PRISMA FLOW CHART



6.4. APPENDIX 4-A: TEMPLATE FOR INCLUDED STUDIES BASELINE CHARACTERSTICS

Age as mean (SD, median, or range: Intravenous iron/control or oral iron	*Female Sex: Intravenous iron/control or oral iron*	*Baseline hemoglobin (g/L) in Intravenous iron group*	*Baseline hemoglobin (g/L) in control or oral iron group*	*Baseline ferritin (mcg/L) in Intravenous iron group*	*Baseline ferritin (mcg/L) in control or oral iron group*

6.5. APPENDIX 4-B: TEMPLATE FOR INCLUDED STUDIES DESCRIPTION

Study and year	*Country*	*Surgery type*	*Patients number: Intravenous iron/control or oral iron*	*Anemic Patients were recruited*	*Comparator*	*Intravenous iron dosage regimen*	*Last follow-up time*

6.6. APPENDIX 4-C: TEMPLATE FOR INCLUDED STUDIES RESULS POST-TREATMENT

Transfusion rate: Intravenous iron vs. control or oral iron	*Hemoglobin (g/L): Intravenous iron group vs. control or oral iron*	*Ferritin* (ng/mL): *Intravenous iron group vs. control or oral iron*	*Incidence of adverse effects in Intravenous iron group vs. control or oral iron*	*Infection (%): Intravenous iron vs. control or oral iron*	*Mortality (%): Intravenous iron vs. control or oral iron*	*Length of Hospital Stay: Intravenous iron vs. control or oral iron*

6.7. APPENDIX 5: THE COCHRANE COLLABOATION'S TOOL FOR ASSESSING RISK OF BIAS

Source of bias	***Review authors' judgment***	***RCT # 1***	***RCT # 2***	***RCT #3…….***
Random sequence generation	Selection bias due to inadequate generation of a randomized sequence	low/unclear/high	low/unclear/high	low/unclear/high
Allocation concealment	Selection bias due to inadequate concealment of allocations before assignment	low/unclear/high	low/unclear/high	low/unclear/high
Blinding of participants and personnel	Performance bias due to knowledge of the allocated interventions by participants and personnel during the study conduction	low/unclear/high	low/unclear/high	low/unclear/high
Blinding of outcome assessment	Detection bias due to knowledge of the allocated interventions by outcome assessment	low/unclear/high	low/unclear/high	low/unclear/high
Incomplete outcome data	Attrition bias due to amount, nature, or handling of incomplete outcome data	low/unclear/high	low/unclear/high	low/unclear/high
Selective reporting	Reporting bias due to selective outcome reporting	low/unclear/high	low/unclear/high	low/unclear/high
Other sources of bias	Bias due to problems not covered elsewhere in the table.	low/unclear/high	low/unclear/high	low/unclear/high

6.8. APPENDIX 6: CHARACTERSTICS INCLUDED STUDIES' TABLES

Table 1: Bernabeu-Wittel et al., 2016

Methods	***Participants characteristics***
Country	Spain
Type of surgery	Hip fracture surgery
Number of participants: Intravenous iron/placebo	103/100
Post-randomization dropout(s):	Three out of 306
*Main age (y): Intravenous iron/*placebo	84.6 ± 6.2/ 82.3 ± 6.9
Female sex (%)	81.5: 87
Intravenous iron: placebo	
Control arm:	Placebo
Inclusion criteria:	Patients of age at least 65 years, osteoporotic HF requiring surgical repair, hemoglobin levels between 90 and 120 g/L, and signed informed consent form.
Exclusion criteria:	Patients with marrow diseases that could interfere in the erythropoietic process, blood coagulation diseases or current treatment with anticoagulants, documented allergy or intolerance and/or contraindication to EPO use and/or IV iron, rheumatoid arthritis and/or another demonstrated origin of inflammatory anemia and/or uncontrolled arterial hypertension, current or previous treatment with EPO or IV iron for at least 3 months, and chronic renal failure receiving hemodialysis or peritoneal dialysis.

Intervention:	Participants were randomly allocated to one of the following groups: Group 2: IV iron arm who received 1000 mg of IV FCM (two 500 mg vials diluted in a bottle of 250 mL of saline, with opaque plastic bag and infusion system), in a 20-min infusion. Group 3: placebo arm who received Subcutaneous single-dose placebo (saline) in a prefilled 1-mL syringe. IV placebo (250 mL of saline, with opaque plastic bag and infusion system), in a 20-min infusion.
Trial's outcomes reported and related to the study primary outcomes:	Outcomes reported were change in hemoglobin levels and blood transfusion requirements.
Time of outcomes measurements:	Hemoglobin levels were measured at 24 and 72 hours after surgery, at discharge, and after 60 days. Transfusion requirement was measured during hospitalization and after 60 days of hospital discharge.
Last follow-up time:	Sixty days post-hospital discharge
Additional notes:	The trial recruited anemic patients. Attempts to contact the trial authors to request more data were unsuccessful.

Table 2: Edwards et al. 2009

Methods	***Participants characteristics***
Country	UK
Type of surgery	Colorectal cancer resection
Number of participants: Intravenous iron/ placebo	34/26
Post-randomization dropout(s):	Not stated
*Main age (y): Intravenous iron/*placebo	Median 67/70
Female sex (%) *Intravenous iron: placebo*	35: 35
Control arm:	Placebo
Inclusion criteria:	Adult patients undergoing bowel resection surgery for colorectal cancer.
Exclusion criteria:	Patients under 18-years old Patients were receiving oral iron in the last six weeks of the day they were approached. Patients received a blood transfusion within that same period. When the surgery time fall within 15 days of date of recruitment.
Intervention:	Participants were randomly allocated to one of the following groups: Group 1: IV iron arm who received 300 mg iron sucrose in 2 infusions separated at least 24 h apart, 14 days pre-surgery. Group 2: placebo arm who received an equal volume of normal saline.

Trial's outcomes reported and related to the study primary outcomes:	Outcomes reported were change in hemoglobin levels and blood transfusion requirements.
Time of outcomes measurements:	Hemoglobin levels were measured at recruitment, pre-surgery surgery, post-surgery, and at discharge. Transfusion requirement was measured post-surgery.
Last follow-up time:	Hospital discharge
Additional notes:	The trial recruited anemic and non-anemic patients. Attempts to contact the trial authors to request more data were unsuccessful.

Table 3: Froessler et al. 2016

Methods	***Participants characteristics***
Country	Australia
Type of surgery	Major Abdominal Surgery
Number of participants: Intravenous iron/placebo	40/32
Post-randomization dropout(s):	Not stated
Main age (y): Intravenous iron/usual care	*64 ± 15 / 68 ±15*
Female sex (%)	53: 47
Intravenous iron: usual care	
Control arm:	Usual care
Inclusion criteria:	Adult patients >18 years with ferritin <300 mcg/L, transferrin saturation <25%, Hb <12.0 g/dL for women, Hb <13.0 g/dL for men.
Exclusion criteria:	Patients under 18-years old.
Intervention:	Participants were randomly allocated to one of the following groups: Group 1: IV iron arm who received ferric carboxymaltose, given as a single dose over 15 minutes, before surgery (simplified dosing protocol; 15mg/kg bodyweight to a maximum dose of 1000 mg). Postoperatively, within two days of surgery, participants received 0.5 mg of ferric carboxymaltose per recorded 1 mL of blood loss, if blood loss was at least 100 ml. Group 2: placebo arm who received usual care.

Trial's outcomes reported and related to the study primary outcomes:	Outcomes reported were change in hemoglobin levels and blood transfusion requirements.
Time of outcomes measurements:	Hemoglobin levels were measured at recruitment, pre-surgery surgery, day post-surgery, and at discharge. Transfusion requirement was measured post-surgery.
Last follow-up time:	Four weeks after surgery.
Additional notes:	The trial recruited anemic patients only. Attempts to contact the trial authors to request more data were unsuccessful.

Table 4: Garrido-Martín et al. 2012

Methods	***Participants characteristics***
Country	Spain
Type of surgery	On-pump cardiac surgery
Number of participants: Intravenous iron/placebo	54/52
Post-randomization dropout(s):	The consort flow chart of the study showed two patients in the IV iron group, and three patients in the placebo group were lost to follow-up.
Main age (y): *Intravenous iron/ placebo*	65 ± 11/ 65 ± 12
Female sex (%) *Intravenous iron: placebo*	30: 23
Control arm:	Placebo.
Inclusion criteria:	Patients older than 18 years of age, elective cardiac surgery under extracorporeal circulation (EC), without previous anemia, susceptible to treatment, without pre- operative blood transfusion, able to complete all study visits per protocol and providing written informed consent.
Exclusion criteria:	Elective cardiac surgery patients without EC, treatment with fibrinolytic therapy 48 h before CPB surgery, history of impaired renal function (creatinine clearance <50 ml/min), previous surgery for active endocarditis, redo-surgery patients, pregnant or lactating, signs of active gastrointestinal bleeding, vitamin B12 deficit, ferropenic anemia, clinical history of asthma or

	allergy, active infection, included in another clinical study, hepatic disease, history of allergy to iron, unlikely to adhere to protocol follow-up, unable to comply with the study protocol.
Intervention:	Participants were randomly allocated to one of the following groups: Group 1: IV iron arm, patients were treated pre- and postoperatively with Intravenous iron (III)-hydroxide sucrose complex (Venofer®; Uriach Lab.) 100 mg of intravenous iron/24 h during pre- and postoperative hospitalization. Group 3: placebo arm, patients were treated pre- and postoperatively with oral and intravenous placebo.
Trial's outcomes reported and related to the study primary outcomes:	Outcomes reported were change in hemoglobin levels and blood transfusion requirements.
Time of outcomes measurements:	Hemoglobin levels were measured at entry operating room exit operating room, ICU admission, ICU discharge, at hospital discharge and at a month of discharge. Transfusion requirement was measured in the operating room, in the ICU, and in the cardiac ward.
Last follow-up time:	One month after discharge.
Additional notes:	The trial recruited non-anemic patients. Attempts to contact the trial authors to request more data were unsuccessful.

Table 5: Johansson et al. 2015

Methods	***Participants characteristics***
Country	Denmark
Type of surgery	Cardiac surgery
Number of participants: Intravenous iron/placebo	26/25
Post-randomization dropout(s):	In the patient disposition chart, they mentioned that one patient withdrew his consent, four patients from the IV group and five patients from the placebo group discontinued the trial. The discontinuation was comparable between the two treatment groups (group A: 13 3% [4/ 30]; group B: 16 7% [5/30]).
Main age (y): Intravenous iron/ placebo	65 ± 8/ 65 ± 11
Female sex (%)	13: 13
Intravenous iron: placebo	
Control arm:	Placebo
Inclusion criteria:	Adult patients undergoing elective or sub-acute CABG, valve replacement or a combination with a Hb ≥12 0 g/dl for women and a Hb ≥13 0 g/dl for men, and who were willing to provide written informed consent.
Exclusion criteria:	Patients with iron overload or disturbances in utilization of iron (e.g. hemochromatosis and hemosiderosis), s-ferritin >800 ng/ml, known hypersensitivity to any excipients in the investigational drug products, history of multiple allergies, decompensated liver cirrhosis and hepatitis, alanine aminotransferase >3 times normal upper value, acute infections,

	rheumatoid arthritis with symptoms or signs of active joint inflammation, pregnant or nursing women, participation in any other clinical trial where the trial drug had not passed five half-lives prior to screening, untreated vitamin B12 or folate deficiency, other IV or oral iron treatment within four weeks prior to screening visit, erythropoietin treatment within four weeks prior to screening visit, and impaired renal function defined by serum creatinine >150 µmol/L. Patients who received blood transfusion <30 days before screening and/or during the surgery were excluded from participation in the trial.
Intervention:	Participants were randomly allocated to one of the following groups: Group 1: IV iron arm who received isomaltoside 1000 mg as a single-dose infusion of 1000 mg over 15 min with a maximum single dose of 20 mg/kg. Group 2: placebo arm who received saline as a single-dose infusion of 100 ml over 15 min.
Trial's outcomes reported and related to the study primary outcomes:	Outcomes reported were change in hemoglobin levels and blood transfusion requirements.
Time of outcomes measurements:	Hemoglobin and ferritin levels were measured at one day before surgery or same day, at day five post-surgery and four weeks postoperatively. Transfusion requirement was measured post-surgery till four weeks postoperatively.
Last follow-up time:	Four weeks after surgery.
Additional notes:	The trial recruited non-anemic patients. Attempts to contact the trial authors to request more data were unsuccessful.

Table 2: Keeler et al. 2017

Methods	***Participants characteristics***
Country	UK
Type of surgery	Colorectal cancer resection
Number of participants: Intravenous iron/oral iron	2/4 (who did not have surgical resection)
Post-randomization dropout(s):	Not stated
Main age (y): Intravenous iron/oral iron	Median (IQR) 73·8 (67·4–78·6)/74·7 (67·9–80·8)
Female sex (%)	39: 36
Intravenous iron: control /oral iron	
Control arm:	Oral iron
Inclusion criteria:	Anemic patients (at least 10 g/L of hemoglobin below the WHO definition of anemia) who are medically fit for surgery, willing to participate and undergoing elective bowel resection surgery for colorectal cancer without metastasis. Their surgery has to be scheduled at least 14 days from date of planned initiation of iron infusion.
Exclusion criteria:	Female patients who were pregnant, lactating or planning a pregnancy during the course of the study. Patients with known blood, kidney, liver disease, iron overload, or allergic to intravenous iron or related iron products. Anemic patients necessitating urgent transfusion or planned blood donation during the study, or who had prior gastric or intestinal operation.
Intervention:	Participants were randomly allocated to one of the following groups:

	Intravenous iron group: ferric carboxymaltose with a maximum dose of 1000 mg per week and a maximum of 2000 mg during the trial. The total dose was ranged between 1000 mg-2000 mg according to the body weight and the hemoglobin level. If patients required two doses, the second dose was administered at least 7 days after the first dose. Group 2: oral iron arm who received ferrous sulphate 200mg twice daily and was continued until surgery.
Trial's outcomes reported and related to the study primary outcomes:	Outcomes reported were change in hemoglobin levels and blood transfusion requirements.
Time of outcomes measurements:	Hemoglobin levels were measured at recruitment, pre-surgery surgery (on the day of surgery), and post-surgery. Transfusion requirement was measured from the recruitment time till post-surgery.
Last follow-up time:	As a routine postoperative outpatient follow-up appointment about 2–3 months post- hospital discharge.
Additional notes:	The trial recruited anemic patients. Attempts to contact the trial authors to request more data were unsuccessful.

Table 6: Kim et al. 2009

Methods	***Participants characteristics***
Country	South Korea
Type of surgery	Gynecological surgery for menorrhagia
Number of participants: Intravenous iron/oral iron	30/26
Post-randomization dropout(s):	9 (23.1%) patients in the intravenous group and 11(29.7%) patients in the oral iron group.
Main age (y): Intravenous iron/oral iron	42.0 ± 7.4/42.3 ± 8.0
Female sex (%)	100:0
Intravenous iron: control /oral iron	
Control arm:	Oral iron
Inclusion criteria:	Patients having menorrhagia with hemoglobin levels below 9.0 g/dL diagnosed as iron deficiency anemia and scheduled to undergo surgical treatment.
Exclusion criteria:	Anemia from causes other than iron deficiency. Current administration of iron. Previous iron therapy or transfusion within three months. History of hematological disease. Chronic disease not suitable for clinical trial.
Intervention:	Participants were randomly allocated to one of the following groups:

	Group 1: IV iron arm who received 200 mg iron sucrose three times a week starting three weeks prior surgery until target hemoglobin of 10 g/dL was achieved. Group 2: placebo arm who received two ampoules of protein succinylate (80 mg of elementary iron per day) beginning three weeks before surgery until the time of surgery.
Trial's outcomes reported and related to the study primary outcomes:	Outcomes reported were change in hemoglobin levels.
Time of outcomes measurements:	Hemoglobin levels were measured pre-treatment and just prior to surgery.
Last follow-up time:	Hospital discharge
Additional notes:	The trial recruited anemic patients only. Attempts to contact the trial authors to request more data were unsuccessful.

Table 7: Serrano-Trenas et al. 2011

Methods	***Participants characteristics***
Country	Spain
Type of surgery	Hip fracture surgery in elderly patients
Number of participants: Intravenous iron/standard protocolized treatment	99/97
Post-randomization dropout(s):	In the patient flow diagram, authors mentioned that 11 patients died (1 patient before surgery, five patients before discharge, and five patients before check-up and patient departure). From the control group, 1o patients died (3 patients before surgery, five patients before discharge, and two patients before check-up and patient departure).
Main age (y): Intravenous iron/standard protocolized treatment	83.46 ± 7/ 82 ± 6
Female sex (%)	80: 79
Intravenous iron: standard protocolized treatment	
Control arm:	The standard protocolized treatment
Inclusion criteria:	Patients aged over 65 undergoing hip fracture surgery.
Exclusion criteria:	Patients diagnosed before the admission of patient (iron overload disorders, hyper- sensitivity to oral or parenteral iron preparations, asthma or other severe atopic, active infection or neoplasm), treatment with clopidogrel or with acetylsalicylic acid at dose rates greater than 150 mg/24 hour, no surgical indication for the current fracture, disorders impaired coagulation (partial

	thromboplastin time > 2.5%, international normalized ratio > 1.5), liver disorders with elevated trans- aminases (aspartase aminotransferase [AST] > 70 U/L, alanine aminotransferase [ALT] > 55 U/L), and chronic kidney failure (creatinine > 2 mg/dL) or patients including in dialysis. No one of their patients refused the transfusion.
Intervention:	Participants were randomly allocated to one of the following groups: Group 1: Control arm who received the standard protocolized treatment. Group 2: IV iron arm who received three doses of 200 mg at 48-hour intervals, starting on the day of admission; administration was by slow perfusion of two 100-mg ampoules diluted in 250 mL of 9% saline solution over a 90-minute period. The first dose was administered in the first 24 hours after admission, always before surgical intervention. The following doses were administered before or after surgery, depending on the time of surgery.
Trial's outcomes reported and related to the study primary outcomes:	Outcomes reported were change in hematocrit, and blood transfusion requirements. We received the data for the hemoglobin change after contacting the first author.
Time of outcomes measurements:	Hematocrit values were measured on admission, at one-day post-surgery, and 7-days postoperatively. Transfusion requirement was measured post-surgery till four weeks postoperatively.
Last follow-up time:	Hospital discharge
Additional notes:	The trial recruited anemic and non-anemic patients We contacted the first author, and he provided us with the hemoglobin data.

Table 8: Shah et al. 2016

Methods	***Participants characteristics***
Country	India
Type of surgery	Gynaecological surgery for menorrhagia
Number of participants: Intravenous iron/oral iron	55/55
Post-randomization dropout(s):	In the patient flow diagram, authors mentioned that 11 patients died (one patient before surgery, five patients before discharge, and five patients before check-up and patient departure). From the control group, 1o patients died (3 patients before surgery, five patients before discharge, and two patients before check-up and patient departure).
Main age (y): Intravenous iron/oral iron	Majority of women were in the age group of 40-49 years (59% and 57% in group A and B respectively).
Female sex (%)	100:0
Intravenous iron: oral iron	
Control arm:	Oral iron
Inclusion criteria:	Patients with Hb less than 10 gm/dl; features of iron deficiency were evidenced by hypochromic microcytic anemia, low MCV, MCH and MCHC values, increased RDW, low serum iron and serum ferritin levels; and women having their surgical procedure at least three to four weeks after preoperative assessment.
Exclusion criteria:	Exclusion criteria were anemia other than iron deficiency; those women requiring early surgery, i.e., women with malignancy; and those unwilling to participate in the study.

Intervention:	Participants were randomly allocated to one of the following groups: Group A: IV iron arm who received 100 mg iron sucrose in 100 ml normal saline by slow IV infusion. The dose was repeated on alternate day basis until target hemoglobin of 10 g/dL was achieved. The treatment either with IV iron or oral iron starts 4-weeks pre-surgery. Group B: Control arm who received ferrous sulphate as oral iron in the dose of one tablet (200 mg salt) three times a day.
Trial's outcomes reported and related to the study primary outcomes:	Outcomes reported were change in Hb levels.
Time of outcomes measurements:	Hemoglobin values were measured pre-treatment and 4-weeks post-treatment (pre-surgery).
Last follow-up time:	Hospital discharge
Additional notes:	The trial recruited anemic patients. Attempts to contact the trial authors to request more data were unsuccessful.

Table 9: Weisbach et al. 1999

Methods	***Participants characteristics***
Country	Germany
Type of surgery	Major orthopedic or cardiovascular surgery
Number of participants: Intravenous iron/ no iron medication	30/30
Post-randomization dropout(s):	Quote: “Of these 123 patients, 90 completed the study. Eight patients dropped out of the study because of acute viral and bacterial infections, two patients did not take oral iron as planned, eight patients refused to continue for reasons unrelated to iron medication, and four patients developed unstable angina or cardiac insufficiency. In 7 patients, ABD could not be continued as planned because of insufficient vein access or severe vasovagal reactions. Four patients dropped out of the study because of suspected side effects of iron therapy as de- scribed below. Overall, 13 patients were excluded from Group 2, 11 from Group 1, and nine from Group 3. Finally, each of the three treatment groups consisted of 15 females and 15 male patients. One female patient in Group 3 who completed ABD did not undergo surgery. This patient was included in the analysis of the preoperative period”.
Main age (y): Intravenous iron/no iron medication	64.4 ± 14.7/64.1 ± 9.5
Female sex (%)	50: 50
Intravenous iron: no iron medication	
Control arm:	No iron medication

Inclusion criteria:	Adult patients (>18years old) scheduled for autologous blood transfusion from Day –49 to Day –35 before major orthopedic or cardiovascular surgery, with a minimum of 3 autologous units scheduled for collection.
Exclusion criteria:	Patients with general contraindications of ABD, evidence of blood loss, renal disease, chronic and acute inflammatory or malignant disorders, pregnancy, lactation or inadequate contraception, myelotoxic therapy as evaluated by clinical history, body weight under 50 kg, initial ferritin <20 µg per L, and a C-reactive protein level over 0.9 mg per dL, or occult gastrointestinal blood loss.
Intervention:	Participants were randomly allocated to one of the following groups Group 2: IV iron arm who received 200 mg of iron sucrose, given after each donation. At enrolment, at least one week before the first donation, an initial IV iron dose was given to fill iron stores, to optimize iron availability in patients with a Hb level below 15 g per dL Group 3: IV control arm who received no iron medication.
Trial's outcomes reported and related to the study primary outcomes:	Outcomes reported were change in hemoglobin levels and blood transfusion requirements.
Time of outcomes measurements:	Hemoglobin was measured at enrolment, at every donation, and at surgery. Transfusion requirement was measured postoperatively.
Last follow-up time:	Hospital discharge
Additional notes:	The trial recruited non-anemic patients. Attempts to contact the trial authors to request more data were unsuccessful.

6.9. APPENDIX 7: THE ETHICAL APPROVAL FORM

Date:	June 5, 2014
Study ID:	Pro00045780
Principal Investigator:	Steven Meyer
Study Title:	Role of perioperative intravenous iron therapy to correct anemia before cardiac surgery: a case series study
Approval Expiry Date:	June 4, 2015

Thank you for submitting the above study to the Health Research Ethics Board - Health Panel. Your application, including revisions received May 15, 22 and June 3, 2014, has been reviewed and approved on behalf of the committee.

The Health Research Ethics Board assessed all matters required by section 50(1)(a) of the Health Information Act. It has been determined that the research described in the ethics application is a retrospective chart review for which subject consent for access to personally identifiable health information would not be reasonable, feasible or practical. Subject consent therefore is not required for access to personally identifiable health information described in the ethics application.

In order to comply with the Health Information Act, a copy of the approval form is being sent to the Office of the Information and Privacy Commissioner.

A renewal report must be submitted next year prior to the expiry of this approval if your study still requires ethics approval. If you do not renew on or before the renewal expiry date (June 4, 2015), you will have to re-submit an ethics application.

Approval by the Health Research Ethics Board does not encompass authorization to access the patients, staff or resources of Alberta Health Services or other local health care institutions for the purposes of the research. Enquiries regarding Alberta Health approvals should be directed to (780) 407-6041. Enquiries regarding Covenant Health approvals should be directed to (780) 735-2274.

Sincerely,

Anthony S. Joyce, Ph.D.

Chair, Health Research Ethics Board - Health Panel

Note: This correspondence includes an electronic signature (validation and approval via an online system).