

The Impact of Preoperative Intravenous Iron Therapy on Perioperative Outcomes in Cardiac Surgery: A Systematic Review

Kelly A. Tankard^a, Brian Park^a, Ethan Y. Brovman^b, Angela M. Bader^{a, c},
Richard D. Urman^{a, c, d}

Abstract

Background: Anemia is common in cardiac surgery affecting 25-40% of patients and associated with increased blood transfusions, morbidity, mortality, and higher hospital costs. Higher rates of stroke, acute renal injury, and total number of adverse postoperative outcomes have also been reported to be associated with preoperative anemia. This systematic review assessed the current evidence for preoperative intravenous iron on major outcomes following cardiac surgery.

Methods: Outcome measures included postoperative hemoglobin, transfusion rates, major adverse events, and mortality. The review was conducted according to Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines, and articles were identified using PubMed, Cochrane, CLINAHL, WOS, and EMBASE databases. Articles were included if they compared patients with and without preoperative anemia based on treatment with intravenous iron. Quality was assessed using Cochrane Risk of Bias Tool and Newcastle-Ottawa scale, and strength of evidence was assessed using the Grading of Recommendations, Assessment, Development and Evaluations (GRADE) approach.

Results: Of the articles reviewed, six met inclusion criteria. These included four randomized double-blind prospective cohort studies, one randomized non-blinded prospective study, and one non-randomized non-blinded prospective study with historical control. Across studies, 1,038 patients were enrolled. Two studies showed higher hemoglobin

with iron therapy, and only one study showed significant differences in multiple outcomes such as transfusion and morbidity.

Conclusions: Given the paucity of studies and biases within them, the current evidence for treatment with intravenous iron prior to cardiac surgery is weak. More evidence is needed to support the administration of preoperative intravenous iron in cardiac surgery patients.

Keywords: Anemia; Cardiac surgery; Iron; Infusion; Preoperative; Outcomes; Intravenous

Introduction

Anemia is common in cardiac surgical patients and is estimated to affect 25-40% of these patients [1-3]. The most common types of anemia seen in cardiac surgery are iron-deficiency anemia (up to 80% of all causes of anemia in cardiac surgery patients), anemia of chronic disease, and hospital-acquired anemia [2, 3]. Prior studies have shown that preoperative anemia is associated with increased blood transfusions, morbidity, mortality, and higher hospital costs [4-15]. Higher rates of stroke, acute renal injury, and total number of adverse postoperative outcomes have also been reported to be associated with preoperative anemia in cardiac surgery patients [13, 14].

Several studies have demonstrated the benefits of pharmacologic treatment of anemia with supplemental iron prior to non-cardiac surgery both in patients with iron-deficiency anemia and those without. In a prospective study, Diez-Lobo and colleagues showed that women with iron-deficiency anemia who received intravenous (IV) iron treatment 2 - 4 weeks before an abdominal hysterectomy had a 2.2 g/dL increase in preoperative hemoglobin (Hb) and 32% decrease in transfusion rates [16]. Froessler and colleagues performed a randomized controlled trial which showed that a single dose of IV iron in patients with iron-deficiency anemia before abdominal surgery reduced transfusion rates by 60% and shortened hospital length of stay by 2.7 days [17]. The intervention group had higher Hb levels prior to surgery and these levels increased to a greater degree 4 weeks after surgery. Cuenca and colleagues evaluated patients undergoing hip fracture surgery, regardless of whether they had iron-deficiency anemia preoperatively and

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^aDepartment of Anesthesiology, Perioperative and Pain Medicine, Brigham and Women's Hospital, Harvard Medical School, 75 Francis St, Boston, MA 02115, USA

^bDivision of Cardiac Anesthesiology, Department of Anesthesiology and Perioperative Medicine, Tufts Medical Center, Tufts University School of Medicine, 800 Washington St, Boston, MA 02111, USA

^cCenter for Surgery and Public Health, Brigham and Women's Hospital, Boston, MA 02115, USA

^dCorresponding Author: Richard D. Urman, Department of Anesthesiology, Perioperative and Pain Medicine, Center for Perioperative Research, Brigham and Women's Hospital, 75 Francis Street, Boston, MA 02115, USA.
Email: ruman@bwh.harvard.edu

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found that preoperative IV iron administration was associated with a decrease in overall infection rates [18].

As mentioned, anemia is estimated to be present in 25-40% of cardiac surgery patients, and cardiac surgery itself is associated with a high rate of transfusion [1, 2, 19-22]. Loor et al had previously shown that cardiac surgical patients with anemia who require transfusion have higher morbidity and mortality [23]. Preoperative anemia in cardiac surgery patients may be due to several mechanisms. Ineffective red blood cell production secondary to chronic inflammation from the underlying pathology causes decreased production of and response to erythropoietin (EPO) in the bone marrow (anemia of chronic disease), inadequate storage of iron (absolute iron deficiency) or utilization of iron (functional iron deficiency) [24]. In a recent review on perioperative anemia management in cardiac surgery, Meybohm et al recommended that preoperative iron-deficiency anemia in cardiac surgery patients be corrected prior to surgery by the supplementation of iron in these patients [3]. They base this recommendation on the low risk profile of iron therapy and the high prevalence of anemia in cardiac surgery patients, although they do not do a full literature review of the current data as we offer in our systematic review.

However, the data on the use of IV iron supplementation for cardiac surgery patients are less robust than in other surgical subspecialties due to the limited number of randomized controlled trials and a lack of adequately powered studies.

Therefore, we performed a systematic review to assess and describe the current evidence of clinical efficacy and impact on patient outcomes of IV iron therapy as a prophylactic treatment of anemia in patients undergoing cardiac surgery. Our goal was to examine the quality of existing evidence on IV iron supplementation for preoperative anemia management. Understanding the current evidence could help clinicians design new clinical care pathways, IV iron clinics [25], and help understand the impact of anemia on patient and hospital outcomes, highlighting the interventions and resources needed to improve care of the cardiac surgical patient.

Materials and Methods

Protocol and registration

This systematic review was performed according to Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [26]. A research librarian (David Osterbur, Countway Library of Medicine, Boston, MA) assisted in developing the protocol which was filed for registration through PROSPERO (submission identification number: 153900) at <http://www.crd.york.ac.uk/PROSPERO>.

A search of PubMed, Cochrane, CLINAHL, WOS, and EMBASE was performed on September 20, 2019 for all publications to date. The search term list (Supplementary Material 1, www.thejh.org) included the following terms: anemia, anemias, anemic, hemoglobin, or hematocrit; and preoperative, preoperative care, presurgical, presurgery, perisurgical, perisurgery, postoperative period, or postoperative care; iron, he-

matinics, antianemic agent, antianemic drug, antianemic factor, or antianemic therapy; and outcome assessment, outcome and process assessment, treatment outcome, patient outcome assessment, or outcome(s); not sickle cell anemia or sickle cell anemia or sickle.

The filters used to condense the results included human studies, English texts only, and type of publication such that case reports, abstracts, editorials, and comments were removed. Duplicate publications were also removed. Additional articles identified by other means were included such as clinical trial registrations identified with published results.

Inclusion/exclusion criteria

Included studies were limited to those that described patients undergoing cardiac surgery. Both prospective and retrospective studies were included. The literature review included studies in patients who were over 18 years of age and who received IV iron in the preoperative setting. Figure 1 shows the study flow diagram depicting inclusion and exclusion criteria and the overall literature selection process used.

Study selection and data extraction

The publications included were selected via a systematic review. All citations using the above search terms in our selected databases were collated using Covidence software (Melbourne, Australia) [27]. All titles and abstracts were screened by one reviewer (BP) to determine eligible studies. Two reviewers (AB and RU) read the full text of each article that made it past the initial phase and independently decided if each publication should be included. Disagreements were resolved by consensus. After this, the first reviewer (BP) recorded the reasons for excluding each article which did not make it to this phase to determine validity of choices. When a final set of studies was chosen based on the above methods, one reviewer extracted data (BP) and another (KT) verified the data. The data we extracted included the name of the author(s), year of publication, design of the study, population characteristics, intervention(s), comparator(s), and outcome(s).

Outcomes

Our primary outcome of interest was change in Hb. The secondary outcomes of interest were transfusion rates, morbidity, safety, length of hospital stay, and mortality.

Data analysis

Once the included studies were chosen, we performed a qualitative analysis. We were unable to perform a meta-analysis due to the limited number of available studies. We present here a summary of the study characteristics, interventions, outcomes and associations, and limitations presented by these publica-

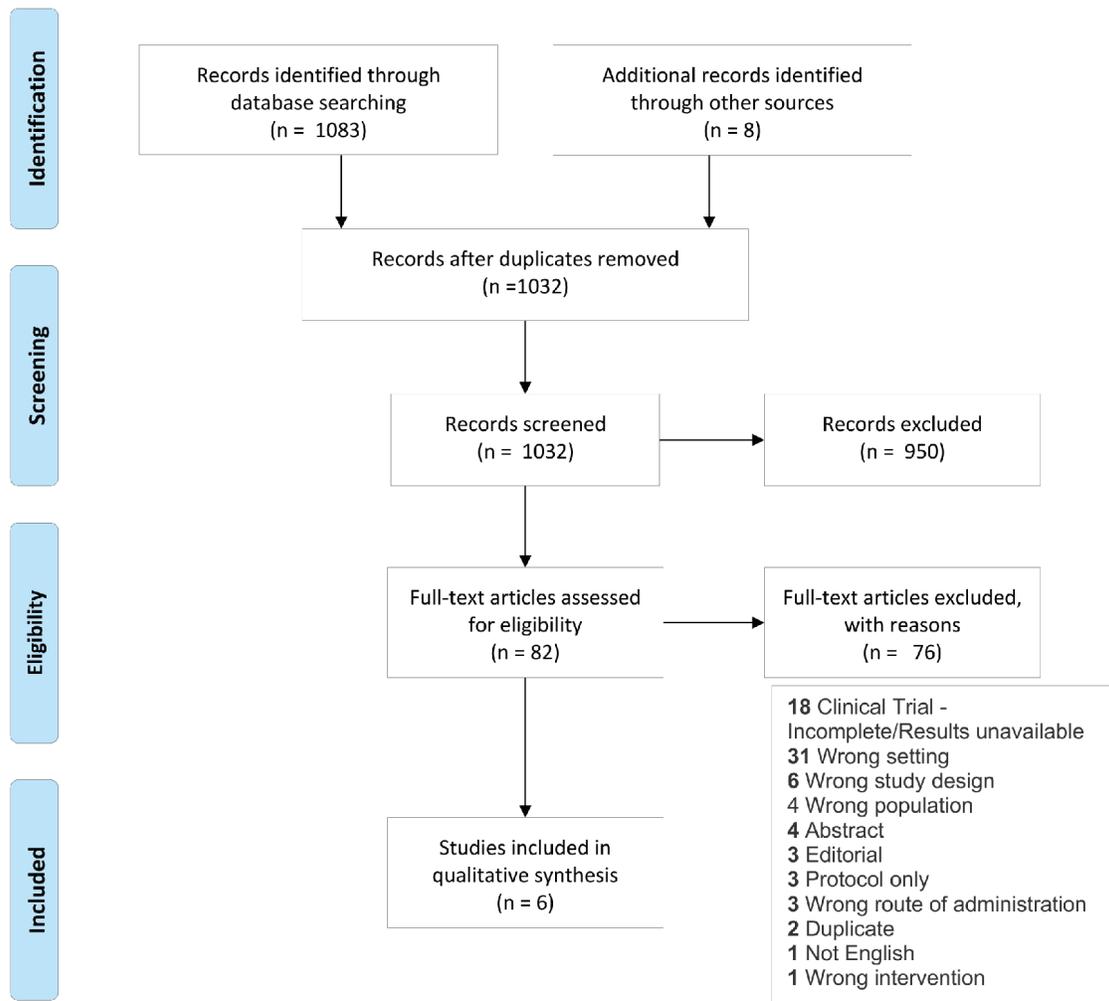


Figure 1. Study flow diagram showing literature selection criteria used for the systematic review.

tions via our qualitative analysis.

Quality assessment

For the four randomized studies, quality was assessed using the Cochrane Risk of Bias Tool [28]. This scale is used to assess bias in randomized studies and includes rankings of “high,” “low,” or “unclear.” Studies are ranked on selection bias which is subcategorized as random sequence generation and allocation concealment; reporting bias which is referred to as selective reporting; other sources of bias; performance bias which is referred to as blinding of participants and personnel; detection bias which is referred to as blinding of outcome assessment; and attrition bias which is referred to as incomplete outcome data [28]. We defined study quality as “good” if the study had no “high” ratings for risk of bias. We defined the study quality as “fair” if the study had 1 - 2 “high” ratings for bias. We defined the study quality as “poor” if the study had 3 or more “high” ratings.

For the one non-randomized study, quality was assessed via the Newcastle-Ottawa scale. This scale is a tool to assess quality via a scoring system which rates studies based on selection, comparability, and outcome [29]. We defined study quality as “good” if the study scored in the ranges of 3 - 4 for selection, 1 - 2 for comparability, and 2 - 3 for outcome. We defined study quality as “fair” if the study scored 2 for selection, 1 - 2 for comparability, and 2 - 3 for outcome. We defined study quality as “poor” if the score did not meet criteria for either “good” or “fair.”

In an effort to decrease potential bias in study selection, we used the above criteria for inclusion and exclusion, performed multiple reviews, and reviewed reasons for exclusion of certain publications. Two reviewers independently assessed each study quality using the above scales and disagreements were resolved by consensus. We did not exclude studies based on how anemia was defined, sample size, or quality of the study. We used the Grading of Recommendations, Assessment, Development and Evaluations (GRADE) criteria to score each publication based on the quantity and quality of studies and

how consistent the findings were [30, 31].

Results

Literature search

A total of 1,083 articles were identified and reviewed. Of the 1,032 unique publications which were screened, 950 were excluded, and 82 full-text studies were assessed for eligibility. Of those, 76 were excluded, and six articles remained which met the criteria for this review (Fig. 1).

Study characteristics

Study characteristics for the six publications we identified can be found in Table 1 [32-37]. All included studies reported pre- and post-intervention Hb levels for iron therapy in the preoperative setting.

The studies were all conducted outside of the USA, with two being done in Spain, one in Canada, one in the UK, one in Denmark, and one in Switzerland [32-37]. The earliest publication year of the studies included was 2012. We included four single center, randomized, double-blinded prospective cohorts, one single center non-blinded non-randomized prospective cohort, and one single center non-blinded randomized prospective cohort. Across the six studies, there were 1,038 patients included. Four of the studies looked only at patients who had been diagnosed with preoperative anemia while the other two studies looked at only non-anemic patients at baseline. Four studies assessed patients undergoing either coronary artery bypass grafting (CABG) and/or valve replacement (VR) using cardiopulmonary bypass (CPB); one study looked only at VR on CPB, and one study looked only at interventional transcatheter VR without CPB. Given the limited number of studies, interventional approaches were not excluded. Three of the studies administered EPO along with iron as part of the intervention arm while three studies administered only iron. Each study administered iron intravenously at different times, ranging from 4 weeks preoperatively to 1 day preoperatively. The total doses of iron varied between studies, ranging from 1 - 5 total doses. Three studies used iron sucrose, one used iron isomaltose, and two used ferric carboxymaltose. Two studies compared the use of IV iron to oral iron therapy whereas the other four studies compared to placebo or historical control.

Definitions and measures

All of the studies defined anemia as Hb < 12 g/dL in women and < 13 g/dL in men in accordance with the World Health Organization (WHO) definition [38]. One study defined transfusion threshold as Hb < 7 g/dL, one defined it as < 7 g/dL or Hb 7 - 8 g/dL with symptomatic anemia, one defined it as < 7 - 8 g/dL intraoperatively and in the intensive care unit (ICU) or Hb < 8 g/dL on the inpatient ward, one defined it as < 8 g/dL if undergoing CABG or < 7 g/dL if undergoing only VR without

CABG, and two studies did not define their transfusion thresholds. One study included intraoperative transfusion as part of their total transfusion requirement measurement, while the rest measured only the need for postoperative transfusion. Four studies included only patients who were anemic at baseline based on the above definition (regardless of the type of anemia) [32, 33, 35, 37]. Two of the studies only studied patients who were non-anemic at baseline by the above definition [34, 36].

Quality of included studies and risk for bias

The grading scheme by domain for each article is specified in Tables 2 and 3 [32-37]. Four studies were of good quality, one article was of fair quality, and one was of poor quality. The poor-quality publication was ranked as such due to high risk of bias for blinding and other sources of bias. The four articles of good quality had low risk of bias in blinding, randomization, and other sources of bias. The study which was of fair quality was the only non-randomized study we included in this review.

Strength of evidence

The reported outcomes in this review were scored using the GRADE criteria. The evidence for Hb, transfusion rate, significant adverse events, infections, length of stay, and mortality were scored as Level 1b and of moderate quality. Reporting quality of life (QOL) as an outcome was scored as Level 2b and of low quality. The results are summarized in Table 4 [32-37].

Association of iron therapy with Hb levels

Hb level before and after preoperative iron therapy were compared to assess the efficacy of this treatment (Table 5 [32-37]). Only one study reported significant difference in Hb between treatment and control groups after treatment. The study by Spahn et al [37], which included patients with anemia at baseline, reported a significant difference in Hb between groups on postoperative day 5 and day 7. Urena et al [34] did not find any significant difference in Hb levels between groups (intervention: 10.7 ± 1.2 g/dL to 10.9 ± 1.2 g/dL; control: 11.3 ± 1.6 g/dL to 11 ± 1.2 g/dL) from baseline; and this was the only study included in this review that looked only at transcatheter VR rather than VR via open surgery on cardiopulmonary bypass. Urena et al [34] only enrolled patients who were anemic at baseline and the intervention included EPO administration with iron treatment. Garrido-Martin et al [33] found no significant difference in Hb levels between the IV iron (14.0 ± 1.63 g/dL to 12.7 ± 1.63 g/dL) and placebo (14 ± 1.35 g/dL to 12.8 ± 1.29 g/dL) groups of patients without iron-deficiency anemia. This study also had a third comparator which was treatment with oral iron; this also showed no significant difference in Hb levels (13.7 ± 1.46 g/dL to 12.6 ± 1.70 g/dL) between either the IV iron or the control group. Johansson et al [36] did not report a significant change in Hb level in the intervention group (14.3 to 12.4 g/dL) 28 days after treatment compared to the placebo group (14.0 g/dL to 11.6

Table 1. Study Characteristics

Author (location)	Cladellas et al, 2012 [32] (Spain)	Urena et al, 2017 [34] (Canada)	Johansson et al, 2015 [36] (Denmark)	Padmanabhan et al, 2018 [35] (UK)	Garrido-Martin et al, 2012 [33] (Spain)	Spahn et al, 2019 [37] (Switzerland)
Design	Single center non-blinded non-randomized prospective cohort with historical control	Single center randomized double-blind prospective cohort	Single center randomized double-blind prospective cohort	Single center non-blinded randomized prospective cohort	Single center randomized double-blind prospective cohort	Single center randomized, double-blind prospective cohort
Population	Mean age (years) Anemia Surgery type N	81 Yes ^a VR, TAVI 100	65 No ^a CABG, VR 60	74 Yes ^a CABG, VR 50	65 No CABG, VR 210	68 Yes ^a CABG, VR 484
Intervention	IV iron Dose Treatment duration EPO	Iron sucrose 200 mg weekly × 2 doses 4 weeks (once per week plus 1 dose 48 h pre-op) Yes ^b	Iron isomaltose 1,000 mg × 1 dose 1 day pre-op No	Ferric carboxymaltose 1,000 - 2,000 mg, 1 - 2 doses 3 - 8 weeks No	Iron sucrose 100 mg × 3 doses 1 week No	Ferric carboxymaltose 1,000 mg × 1 dose 1 day pre-op Yes
Comparator	Historic observation	Placebo	Placebo	PO Fe fumarate (200 mg) BID	PO iron fumarate (105 mg) or placebo	Placebo
Outcomes	Blood Hb measured baseline, at the start of surgery, initiation of CPB, every 15 min while on CPB, and at the end of VR	Hb 1 day before and within 24 h of hospital discharge	Hb, ferritin, iron, TSAT, reticulocyte, % anemic	Hb, iron, ferritin, transferrin, C-reactive protein, total iron binding capacity, EPO, achieve > 1.5 g/dL measured at least 3 weeks prior to surgery and again on the day of surgery	Hb, IRF, MCV, ferritin	Hb, reticulocyte, C-reactive protein, calculated RBC loss
Transfusion	Units per patient, number of patients transfused	Units transfused, number of patients transfused within 30 days	Units transfused, number of patients transfused	Units transfused, number of patients transfused	Units/patient, number of patients transfused	Number of units transfused
Safety	Yes	Yes	Yes	Yes	Yes	Yes
Mortality	Yes	Yes (30 day)	Yes	Yes	No	Yes
Other	LOS, HF, CVA, MI, ARF, tamponade, re-op, infection, prolonged ventilation, thrombosis or failure of valve, endocarditis	LOS, peak troponin and CKMB, rates of MI, stroke, AKI, need for HD, and new onset AF	Safety (adverse events, vital signs, ECG, s-phosphate and hematology and biochemistry parameters)	LOS, QOL, AKI, AF, infection	LOS	LOS, infection, CVA, MI, AF, thrombosis, product acquisition costs, duration of mechanical ventilation

^aWHO criteria (Hb < 13.0 g/dL in men or < 12.0 g/dL in women). ^bIV rhEPO at 500 IU/kg/day every week for 4 weeks and the fifth dose 48 h before VR with each session receiving IV iron sucrose (weight-based dosing). ^cTwo weight-based doses of subcutaneous EPO (0.75 µg/kg darbepoetin alfa). AF: atrial fibrillation; AKI: acute kidney injury; ARF: acute renal failure; CABG: coronary artery bypass grafting; CKMB: creatinine kinase-MB; CPB: cardiopulmonary bypass; CVA: cerebrovascular accident; ECG: electrocardiogram; EPO: erythropoietin; Hb: hemoglobin; HD: hemodialysis; HF: heart failure; IRF: immature reticulocyte fraction; LOS: length of stay; MCV: mean corpuscular volume; MI: myocardial infarction; PO: per os; QOL: quality of life; TAVI: trans-aortic valve implantation; TSAT: transferrin saturation; VR: valve replacement; pre-op: preoperatively; re-op: re-operation; BID: twice a day.

Table 2. Evidence Grading With Cochrane Risk of Bias Tool

Author	Random sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment	Incomplete outcome data	Selective reporting	Other sources of bias	Quality
Urena et al, 2017 [34]	Low	Low	Low	Low	Low	Unclear	Low	Good
Johansson et al, 2015 [36]	Low	Low	Low	Low	Low	Unclear	Low	Good
Padmanabhan et al, 2018 [35]	Low	Low	High	High	Low	Unclear	High	Poor
Garrido-Martin et al, 2012 [33]	Low	Low	Low	Unclear	High	Unclear	Low	Good
Spahn et al, 2019 [37]	Low	Low	Low	Low	Low	Unclear	Low	Good

Table 3. Evidence Grading With Newcastle-Ottawa Scale Assessment of Study Quality

Author	Selection	Comparability	Outcome	Total	Quality
Cladellas et al, 2012 [32]	3	1	2	6	Fair

g/dL). Johansson et al excluded patients who were anemic at baseline and those who received transfusion intraoperatively.

Cladellas et al [32] found significantly higher Hb levels in the treatment group (11 g/dL initial, 12.6 g/dL preoperatively) than the control (10.9 g/dL initial and preoperative Hb). Cladellas et al studied EPO given with iron as their treatment group. The placebo group and treatment group were also studied consecutively rather than concomitantly in time.

The study rated as poor by Padmanabhan et al [35] showed no significant change in Hb levels after treatment between groups (IV: 11.9 g/dl to 12.0 g/dl; oral: 11.4 g/dl to 11.8 g/dl). Only patients who were anemic at baseline were enrolled. The study was non-blinded, many of its patients were lost to follow-up, patients in the treatment arm could opt out of the second dose of IV iron, and the study changed its definition of anemia midway through the study to match WHO guidelines.

Association of iron therapy with transfusion rates

All six studies reported differences in transfusion rate as an outcome. These results are summarized in Table 6 [32-37]. Of

the good quality studies, all four found no significant differences in transfusion rates between treatment and control groups. Urena et al [34], Garrido-Martin et al [33], and Johansson et al [36] did not find any significant difference in transfusion rates between groups. Padmanabhan et al [35] whose study we rate as poor quality did not find a significant difference in transfusion rates.

Cladellas et al [32] reported a significant difference in transfusion rates when comparing the treatment arm with the control group. They found a transfusion rate of 67% in the treatment group compared to 93% in the control group ($P < 0.001$). The nadir of Hb levels during cardiopulmonary bypass was significantly higher for patients in the treatment group and treatment was also associated with a lower morbidity and mortality. The number of patients requiring over six units of red blood cells also decreased significantly between groups from 36% in the control group to 4% in the treatment group, which indicates patients in the treatment group were less likely to require massive transfusion.

Spahn et al [37] also reported a significant difference in transfusion rates between the intervention and control group. The transfusion rate was 44% in the treatment group, with a

Table 4. Strength of Evidence

Author	Hb	Transfusion rate	Significant AE	QOL	Infections	LOS	Mortality
Cladellas et al, 2012 [32]	X	X	X		X	X	X
Urena et al, 2017 [34]	X	X	X		X	X	X
Johansson et al, 2015 [36]	X	X	X		X		X
Padmanabhan et al, 2018 [35]	X	X	X	X	X	X	X
Garrido-Martin et al, 2012 [33]	X	X	X		X		
Spahn et al, 2019 [37]	X	X	X		X	X	X
Summary of Level of Evidence ^a	(6) 1b	(6) 1b	(6) 1b	(1) 2b	(6) 1b	(4) 1b	(5) 1b
Quality of Body of Evidence ^b	Moderate	Moderate	Moderate	Low	Moderate	Moderate	Moderate

^aOxford Centre for Evidence-based Medicine's "Levels of Evidence." <https://www.cebm.net/2009/06/oxford-centre-evidence-based-medicine-levels-evidence-march-2009/>; ^bCincinnati Children's Hospital Medical Center Evidence Collaboration's, file:///Users/kellytankard/Downloads/Guideline%20Development%20Manual%20(1).pdf. AE: adverse event; Hb: hemoglobin; QOL: quality of life; LOS: length of stay.

Table 5. Hemoglobin Levels Before and After Preoperative Iron Therapy

Author	Iron	EPO	Hb				Other significant hematologic findings
			Baseline	Pre-op	Post-op	Follow-up	
Cladellas et al, 2012 [32]	IV	IV	11.2 ± 1	12.6 ± 0.9*	-	-	
	Historic observation	Historic observation	10.9 ± 0.9	10.9 ± 0.9	-	-	
Urena et al, 2017 [34]	IV iron sucrose 200 mg at days 10 and 1	Subcutaneous 0.75 µg/kg	10.7 ± 1.2	10.9 ± 1.2*	9.4 ± 1.6 (discharge)	-	No significant difference between pre-op, post-op, or discharge Hb after intervention
	Placebo	Placebo	11.3 ± 1.6	11.1 ± 1.2*	9.9 ± 1.6	-	
Johansson et al, 2015 [36] ^a	IV	None	14.3	-	10.2 (POD 5)	12.4** (POD 28)	More non-anemic on follow-up
	Placebo		14	-	10.5	11.6**	
Padmanabhan et al, 2018 [35]	IV	None	8.9	9.8	-	-	Increase in ferritin, decrease in EPO, TSAT
	Oral		11.1	12	-	-	
Garrido-Martin et al, 2012 [33]	IV	None	14 ± 1.63	12.7 ± 1.64	11.1 ± 1.52 (POD 10)	12.7 ± 1.40 (POD 30)	Higher ferritin
	Oral		13.7 ± 1.46	12.6 ± 1.70	11.0 ± 1.28	12.4 ± 1.27	
	Placebo		14 ± 1.35	12.8 ± 1.29	11.0 ± 1.44	12.3 ± 1.15	
Spahn et al, 2019 [37]	IV	Subcutaneous 40,000 units	12.8 ± 1.5	-	9.2*** (POD 5)	9.1*** (POD 7)	Higher reticulocyte count
	Placebo		12.9 ± 1.5	-	8.7***	8.5***	

*P < 0.05 between groups; **P < 0.05 from baseline; ***P < 0.001 between groups; ^aSD not reported. EPO: erythropoietin; Hb: hemoglobin; IV: intravenous; pre-op: preoperatively; POD: postoperative day; post-op: post-operatively; TSAT: transferrin saturation; SD: standard deviation.

median of 0 units (interquartile range (IQR): 0 to 2) transfused, compared to 53% transfusion rate in the control group (P < 0.05), with a median of 1 unit (IQR: 0 - 3) transfused. The transfusion rates for platelets and fresh frozen plasma were also measured during the same 7-day period, but not found to be significantly different between groups.

Association of iron therapy with other clinical outcomes

Results of secondary outcomes can be seen in Table 7 [32-37]. Four studies compared length of stay between groups. Urena et al [34] was the only publication of good quality which measured length of stay and found no difference between groups. Cladellas et al [32] which we rate as fair quality studied length of stay and found there to be a significantly shorter admission (P < 0.01; 10 days, IQR: 8 - 14; 15 days, IQR: 10 - 27) in patients who received IV iron. Padmanabhan et al [35] whose study we rank as poor quality found no difference in length of stay between groups.

Five studies assessed mortality between groups. Cladellas et al [32] was of fair quality and did find a significant difference in mortality with a 9% mortality rate in the treatment group compared to a 23% mortality rate in the control group (P = 0.04). The five other studies in this review reported no mortality difference between groups.

All studies assessed infection rates between treatment and

control groups. Cladellas et al [32] which was of fair quality was the only study which showed a significant difference between groups. They reported an 8% incidence of infections in the treatment group versus 24% in the control group (P = 0.01). The five other studies did not find any significant difference of infection rates between groups.

One study assessed QOL between groups. Padmanabhan et al [35] did not find a significant difference in QOL between groups as measured by the modified Short Form-36 and EUROQOL-5D questionnaires.

All studies recorded adverse events. None of the studies reported significant differences between groups regarding adverse events as defined by each individual study.

Discussion

Anemia in cardiac surgery has previously been shown to be a risk factor for increased need for transfusions, adverse outcomes, mortality, and higher costs to the patient and hospital system [1, 2, 4, 8, 11]. The use of IV iron therapy preoperatively has been studied in other surgical subspecialties with promising results; however its use in cardiac surgery has been poorly defined [16-18]. Shin et al who published a systematic review in 2019, showed that the current evidence for iron therapy preoperatively in orthopedic surgery patients supports its use to decrease number of transfusions, length of stay, and infections

Table 6. Association of Iron Therapy With Transfusion Rate

Author	Intervention	Transfusion		
		Transfusion trigger	Transfusion rate, n/N (%)	Median number of units transfused
Cladellas et al, 2012 [32]	IV iron + IV EPO	Hb < 7 g/dL	50/75 (67)	NR
	Historic observation		55/59 (93)**	NR
Urena et al, 2017 [34]	IV iron + IM EPO	Hb < 7 g/dL, Hb 7 - 8 g/dL if symptomatic	13/48 (27)	1
	Placebo		13/52 (27)	2
Johansson et al, 2015 [36]	IV	NR	8/30 (27)	1
	Placebo		11/30 (37)	2
Padmanabhan et al, 2018 [35]	IV	NR	16/20 (80)	1.5
	Oral		12/20 (60)	2
Garrido-Martin et al, 2012 [33]	IV	Hb < 8 g/dL in coronary patients, Hb < 7 g/dL in valve surgery patients	20/54 (37)	0
	Oral		27/53 (51)	1
	Placebo		26/50 (50)	0.5
Spahn et al, 2019 [37]	IV + SC EPO	Hb < 7 - 8 g/dL intraoperative and ICU, Hb < 8 g/dL on wards	108/243 (44)	0
	Placebo		127/241 (53)*	1

*P < 0.05 between groups; **P < 0.001 between groups. Hb: hemoglobin; IV: intravenous; IM: intramuscular; NR: not reported; EPO: Epogen; SC: subcutaneous; ICU: intensive care unit.

although without changing mortality [39]. The goal of our paper was to review the current evidence regarding the use of preoperative iron therapy in cardiac surgery. Our review is the most recent and comprehensive on this topic, and we conclude that more work needs to be done to elucidate whether there is significant benefit from treating cardiac surgery patients with preoperative iron. Hogan et al published a systematic literature review in 2014 looking at the effects of anemia on outcomes in cardiac surgery [40]. Although they reported some of the same studies, their search included preoperative and postoperative iron administration, including co-administration of EPO. Our review is focused on iron therapy as a preoperative intervention and its effects on outcomes after cardiac surgery.

Three of the six studies (Johansson et al [36], Cladellas et al [32], and Spahn et al [37]) found significantly higher Hb levels in the treatment group than the control group. However, the studies included were of mixed quality and at most of mod-

erate quality evidence. There currently remains a lack of strong evidence for IV iron therapy in optimizing Hb levels prior to cardiac surgery.

Cladellas et al [32] and Spahn et al [37] found a significant difference in transfusion rates in the treatment group. However, Cladellas et al [32] was the only study to find significant differences in secondary outcomes. Anemic patients were found to have a greater than three-fold increase in the odds of death and four-fold increase in odds of major complications. There was a significant decrease in acute renal failure, congestive heart failure, prolonged intubation, and composite morbidity in the treatment group.

There are several possible explanations for the differences across studies. The dosage, duration, and formulation of iron therapy differed across studies. The studies reporting no significant difference in outcomes with iron therapy address this discrepancy by discussing the possibility of not having admin-

Table 7. Other Outcomes

Author	Surgery	Significant AE ^a	QOL	Infections	LOS, median (IQR)	Mortality
Cladellas et al, 2012 [32]	VR	None	NR	Decreased: 8% vs. 24%, P = 0.01	Shorter: 10 days (8 - 14) vs. 15 days (10 - 27), P < 0.01	Decrease: 9% vs. 23%, P = 0.04
Urena et al, 2017 [34]	VR (TAVI)	No diff	NR	No diff	No diff	No diff
Johansson et al, 2015 [36]	CABG, VR	No diff	NR	No diff	NR	No diff
Padmanabhan et al, 2018 [35]	CABG, VR	None	No diff	No diff	No diff	No diff
Garrido-Martin et al, 2012 [33]	CABG, VR	None	NR	Not increased	NR	NR
Spahn et al, 2019 [37]	CABG, VR	No diff	NR	No diff	No diff	No diff

^aAs defined by study. AE: adverse event; CABG: coronary artery bypass grafting; diff: difference; IQR: interquartile range; LOS: length of stay; NR: not reported; QOL: quality of life; TAVI: trans-aortic valve implantation; VR: valve replacement.

istered IV iron in high enough dose to produce a significant effect. In fact, participants in the study by Padmanabhan et al [35] could opt out of the second dose of iron and therefore only receive one dose of IV iron. The study of Cladellas et al [32], which was the only publication to find significant differences in multiple outcomes, used five doses of IV iron over a 4-week preoperative treatment period and focused on valve repair only. This was the highest number of IV iron doses over the longest period preoperatively of any of the studies. Thus, it is possible that the significance of their findings with iron therapy may have been related to the number of iron doses over a longer period of time preoperatively compared to the other studies. It is possible that other studies may not have given a high enough dose to identify significant differences between groups, or that the broad scope of cardiac surgery introduces more heterogeneity.

Side effects of IV iron, including infection, hypersensitivity, and iron overload, have been reported [3]. One systematic review of IV iron reported infusion reactions at the IV site [41]. However, all six studies in this review reported no adverse events and no significant increase in infection rates between groups. Cladellas et al [32] found a significantly lower rate of infection in the IV iron group compared to historical control. These findings support the current literature citing no significant association between IV iron therapy and increased infection rates [41-45].

There were three types of IV iron formulations used in the reported studies. Three studies involved administration of iron sucrose [32-34]. Johansson et al [36] administered iron isomaltose, while Padmanabhan et al [35] and Spahn et al [37] administered ferric carboxymaltose. Ferric carboxymaltose is reported to have effects from a single dose and has higher maximum concentration per dosage [46]. Few studies compare efficacy of formulation, and none in the cardiac surgery literature. In regard to hypersensitivity reactions, current formulations of IV iron including iron sucrose, iron isomaltose, and ferric carboxymaltose have been shown to be much better tolerated than prior formulations of iron therapy such as iron dextran [47].

Two of the studies assessed the route of iron administration. Garrido-Martin et al [33] and Padmanabhan et al [35] compared iron therapy via the IV route with the oral route, although they did not find any difference between either route or placebo. The use of oral iron may not be as appropriate for use in cardiac surgery, as oftentimes cardiac surgery is urgent and there may not be enough time to reach a therapeutic threshold with oral iron. The IV route has a quicker onset and avoids first-pass metabolism. Oral iron may be less favorable due to gastrointestinal intolerance, and reduced uptake during inflammatory states [48].

The role of EPO and whether it may have impacted results is unclear. It should be noted that three of these studies looked at the concomitant administration of EPO with iron (Cladellas et al [32], Urena et al [34], and Spahn et al [37]), while the three other studies looked at iron therapy alone. Yoo et al recently conducted a study looking primarily at the effect of EPO on patients undergoing cardiac surgery and showed that treatment with a single dose of EPO with a small dose of iron 1 day before surgery reduced transfusion rates [49]. A

recent meta-analysis by Kei and colleagues reported decreased transfusions rates when comparing IV iron with and without EPO, although the sub-group analysis included cardiac and orthopedic surgeries [45, 50]. Theoretic risks of EPO include an increase in thrombosis, although there is a lack of clear corroborating evidence. Furthermore, a recent study showed that patients undergoing cardiac surgery receiving EPO showed no differences in thrombosis, infection, or mortality [51].

A notable difference among studies is the state of preoperative anemia. Most of the studies investigated patients who were anemic at baseline (regardless of type of anemia); however Johansson et al [36] and Garrido-Martin et al [33] studied only non-anemic patients. Many cardiac surgery patients are anemic at baseline, and it is well established that the Hb level affects transfusion rates and outcomes after cardiac surgery [1-3]. Furthermore, blood management protocols recommend iron therapy for treatment of iron-deficiency anemia [52]. The lack of consistent anemia delineation likely diminishes the study results. Of the four studies which looked only at patients who were anemic at baseline (regardless of type of anemia), the degree of preoperative anemia as measured by baseline Hb was similar across the studies. Thus, we are unable to comment on the efficacy of IV iron based on severity of preoperative anemia in those studies which looked only at anemic patients. Given that the studies looked at patients with all types of anemia, we are unable to comment on the efficacy of treatment with IV iron based on the type of preoperative anemia.

Other methods of reducing rates of transfusion aside from iron therapy include cell salvage intraoperatively, autologous blood transfusions, restrictive institutional blood transfusion guidelines, and decreasing the number of labs drawn in the ICU and postoperatively. A recent review article by Meybohm et al on the management of perioperative anemia in cardiac surgery suggests that “correcting preoperative anemia should be mandatory ahead of planned cardiac surgery” and “preoperative therapy of anemia with parenteral iron is recommended according to current evidence” [3]. The authors based this recommendation on the low risk profile of iron therapy and the high prevalence of anemia in cardiac surgery patients, although they do not do a full literature review of the current data as we offer in our systematic review.

Our review shows that the current state of the evidence on iron therapy prior to cardiac surgery has not yet been clearly defined and more evidence is required to strengthen consensus statements and blood management systems. The six studies we identified via our systematic review are of mixed quality and mixed results with half of the studies showing a significant difference in Hb levels and only one study showing significant differences in transfusion or any other outcome. More work needs to be done to make any definitive conclusions, which can guide consensus guidelines on treatment of cardiac surgery patients preoperatively with IV iron.

Strengths and limitations

Our systematic review has several strengths. We performed a comprehensive search with broad search terms, enlisted methodology expertise, and did not limit the search by time-

frame. We included experimental designs to avoid selection bias. We assessed quality by Cochrane Risk of Bias Tool and the Newcastle-Ottawa Scale Assessment of Study Quality. Our review is currently the most recent and comprehensive on this topic.

One of the significant limitations of our review is the paucity of publications investigating iron therapy as an intervention preoperatively prior to cardiac surgery. We were only able to identify six studies which met our inclusion and exclusion criteria. Of these studies, only four of the six studies were of good quality based on our quality assessment and risk of bias scores, one was of fair quality, and one was poor quality. Results were reported on all studies despite the quality. Nevertheless, strong conclusions could not be drawn from these six studies. Individual studies may not have given high enough doses of the treatment or have been adequately powered to identify significant differences between groups.

The study done by Urena et al [34] was only for percutaneous VR without cardiopulmonary bypass while the other studies looked only at open cardiac surgery on bypass. The blood loss and coagulopathy with cardiopulmonary bypass is much higher than without and thus the study by Urena et al may not be comparable to the other four studies.

The studies included in this paper also differ in whether they included or excluded patients with preoperative anemia which limits the ability to generalize results to all patients regardless of baseline Hb levels.

None of these studies were done in the USA, which may make the results less generalizable to the US hospital system given changes in practice across countries. We excluded studies looking at the pediatric population and those related to sickle cell anemia. There are also ongoing relevant studies, although no published data are yet available [53].

Conclusions

More studies are needed to determine the effect of preoperative iron therapy in cardiac surgery. This is especially important because cardiac surgical patients receive more blood transfusions than those undergoing other types of surgery; and blood transfusion in these patients has been associated with higher morbidity and mortality [54]. Only half of the studies in our review showed higher Hb levels with the use of iron therapy, and only one of the six studies showed significant differences in multiple other outcomes such as transfusion rate and morbidity. The study which showed significant differences in multiple outcomes with iron therapy (Cladellas et al [32]) gave participants the highest dose of iron over the longest period preoperatively, and studied patients undergoing valve repairs. It is possible that the other five studies did not give enough iron over a long enough treatment time to see more significant differences in outcomes, or the data are confounded by the use of bypass in nonvalvular surgeries. More studies are needed to investigate the role of iron in cardiac surgery. Other interventions such as the use of EPO, vitamin B12, and folate may also play a role and offer areas for future investigation as well. The investigation of ways to reduce transfusion rates in cardiac sur-

gery is important in order to decrease costs to both the patient and the hospital. Based on our review of the current literature, we are unable to recommend that patients undergoing cardiac surgery be routinely treated preoperatively with IV iron.

Supplementary Material

Suppl 1. Search terms used in each database.

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Conflict of Interest

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Author Contributions

Each author certifies involvement in data acquisition, manuscript preparation and editing.

Data Availability

Literature search data are available upon request.

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